EVALUATION OF RENAL LESIONS IN RHEUMATOID ARTHRITIS WITH CLINICO-PATHOLOGIC CORRELATION

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CERTIFICATE

This is to certify that this Dissertation entitled "**EVALUATION OF RENAL LESIONS IN RHEUMATOID ARTHRITIS WITH CLINICO-PATHOLOGIC CORRELATION"** is the bonafide original work of **Dr. MUTHU KUMAR. P**, in partial fulfillment of the requirement for D M., (Nephrology) examination of the Tamilnadu Dr.M.G.R Medical University will be held in August 2013.

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DECLARATION

I, **Dr. MUTHU KUMAR. P**, solemnly declare that the dissertation titled "**EVALUATION OF RENAL LESIONS IN RHEUMATOID ARTHRITIS WITH CLINICO-PATHOLOGIC CORRELATION"** is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of Dr.N.GOPALAKRISHNAN M.D.,D.M ,FRCP, Professor of Nephrology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

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CONTENTS

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic crippling disease that affects various organ systems including the kidney. RA is the second most common rheumatologic problem next only to Systemic lupus erythematosus. Renal involvement in RA can be either due to the disease per se or due to the drugs used to treat the condition. RA can affect all the components of the kidney including the glomerulus, tubules, interstitium and the blood vessels. Most of the patients will be taking non-steroidal anti-inflammatory drugs, the potential renal toxicity of which is well known. Gold and penicillamine used in the management of RA has been very well known for their nephrotoxic potential by causing secondary membranous nephropathy. Some patients particularly those residing in the rural areas of Indian sub-continent might take indigenous medicines for the treatment of RA. If these indigenous medicines contain nephrotoxic substances, it adds up to the renal injury. Presence of other comorbidities like hypertension and atherosclerosis also affects the course and prognosis of renal disease in rheumatoid arthritis.

Renal disease in RA is usually asymptomatic and detected only in laboratory investigations. Urine analysis for microalbuminuria, proteinuria, red blood cells and red blood cell cast and blood biochemistry including urea, creatinine and electrolytes still remains as the cost effective tool for screening renal disease in RA. However renal biopsy remains the 'gold standard' investigation for the diagnosis of renal pathology with certainty. Great emphasis has to be placed on regular and periodic screening, because the detection of renal disease early has got two implications. First, most of the drug induced renal lesions resolve spontaneously after prompt cessation of the offending drug; say for an example gold induced membranous

nephropathy. Second, some of the disease modifying anti-rheumatic drugs require dose reduction in the presence of renal failure like methotrexate.

There are various clinical case series and autopsy studies available in the literature highlighting the renal involvement in RA. Most of the studies come either from Japan or from other overseas countries. Except for few case reports, there are not much of Indian studies regarding the renal involvement in RA. This study is intended to evaluate renal lesion in RA among Indian patients in a tertiary care hospital in south India.

AIM OF THE STUDY

- To evaluate renal lesions in patients with Rheumatoid arthritis and to assess the clinicopathologic correlations.

- To assess the course and prognosis of renal diseases in patients with Rheumatoid arthritis.

REVIEW OF LITERATURE

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease of unknown cause. The characteristic feature of established RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The hallmark of the disease is cartilage damage and bone erosions secondary to the synovial inflammation. The course of RA can be quite variable. The disease severity can vary from mild oligoarticular involvement with minimal joint damage to a widespread progressive polyarthritis resulting in marked functional impairment.

EPIDEMIOLOGY AND GENETICS

Rheumatoid arthritis affects about 1% of the population[1], in a female/male ratio of 2·5/1. The prevalence increases with age, and sex differences diminish in the older age group. Onset of the disease is most frequent during the fourth and fifth decades of life, with 80% of all patients developing the disease between the ages of 35 and 50. RA is seen throughout the world and affects all races. However, the incidence and severity seem to be less in rural sub-Saharan Africa and in Caribbean blacks.

Family studies indicate a genetic predisposition. Severe RA is found at approximately four times the expected rate in first-degree relatives. The concordance rate of RA in monozygotic twins varies from 12 to 15%, implying that factors other than genetics play an important etiopathogenic role[2,3]. The major genetic risk factors for RA are located in major histocompatibility complex (MHC) with allelic variation in the HLA-DRB1 gene, which encodes the MHC II beta-chain molecule. Additional genes in the HLA-D complex may also convey susceptibility to RA.

Environmental factors also play a role in the etiology of the disease. Epidemiologic studies in Africa have indicated that climate and urbanization have a major impact on the incidence and severity of RA. Smoking is also an important risk for RA in persons expressing an HLA-beta 1 susceptibility allele.

Various infectious agents has been suggested including Mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus, parvovirus, and rubella virus, but convincing evidence regarding their causative role has not emerged.

PATHOGENESIS

The pathogenic mechanisms of synovial inflammation are likely to result from a complex interplay of genetic, environmental, and immunologic factors that produces dysregulation of the immune system **(Fig.1)**. Precisely what triggers these initiating events and what genetic and environmental factors disrupt the immune system remain a mystery. The earliest pathogenic mechanism identified in RA is breakdown in self-tolerance. This is supported by the finding that autoantibodies, such as rheumatoid factor(RF) and antibodies to cyclic citrullinated peptides (anti-CCPs) may be found in sera from patients long before clinical disease. The pathogenesis of RA is built upon the concept that self-reactive T cells drive the chronic inflammatory response. In the rheumatoid joint, by mechanisms of cell-cell contact and release of soluble mediators, activated T cells stimulate macrophages and fibroblast-like synoviocytes to generate proinflammatory mediators and proteases that drive the synovial inflammatory response and destroy the cartilage and bone. CD4+ T cells also provide help to B cells, which in turn, produce antibodies that may promote further inflammation in the joint. RFs may form large immune complexes inside the joint that contribute to the pathogenic process by fixing complement and promoting the release of proinflammatory chemokines and chemoattractants.

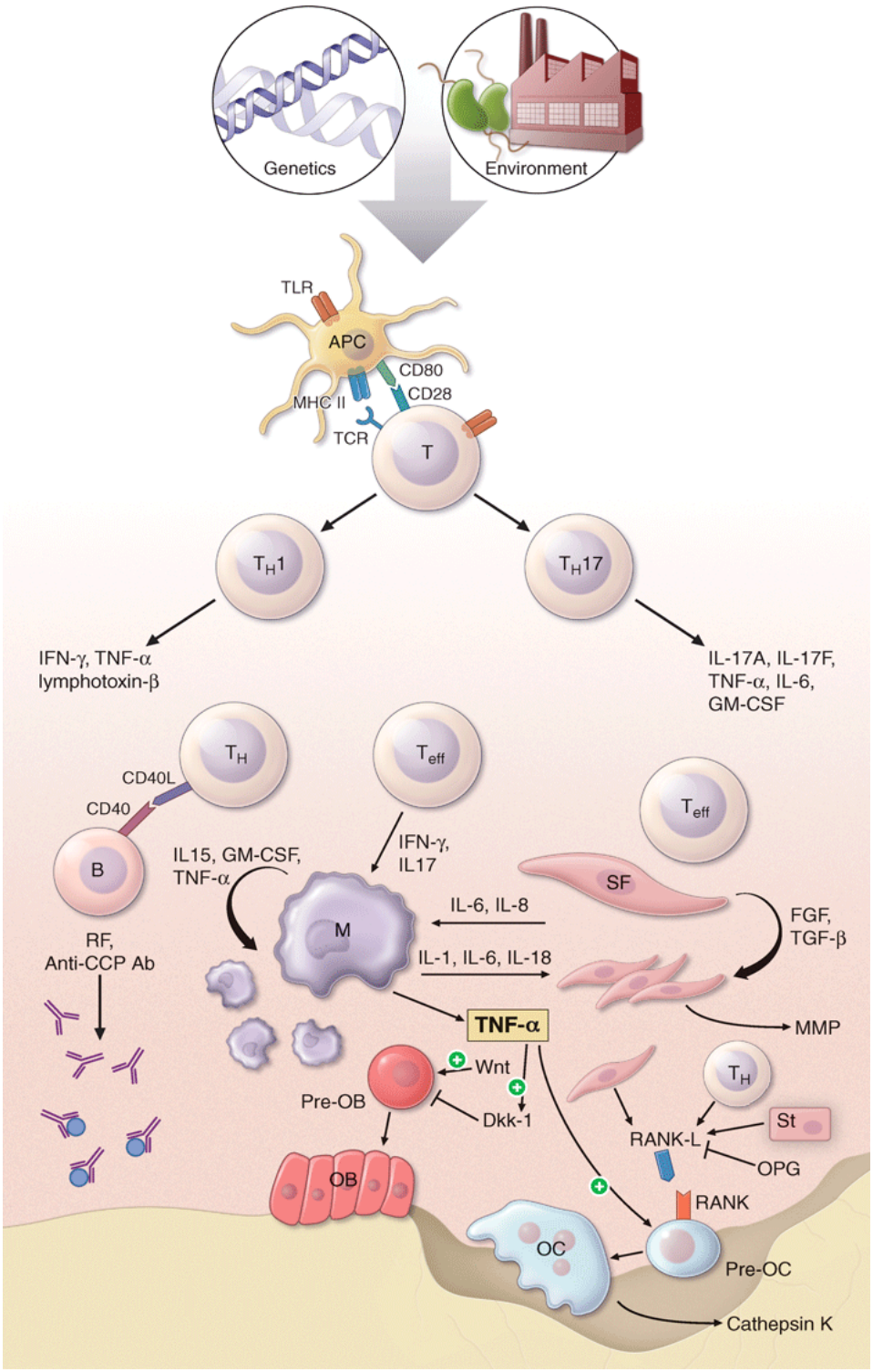

Fig-1: Genetic and environmental factors cause a break in self tolerance and activate auto-reactive T cells that release inflammatory cytokines which in turn stimulate osteoclasts resulting in bone and joint destruction[4].

PATHOLOGY

Rheumatoid arthritis affects the synovial tissue and underlying cartilage and bone. The synovial membrane covers most articular surfaces, tendon sheaths, and bursae. The pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. The structural damage to the mineralized cartilage and subchondral bone is mediated by the osteoclast. Chronic inflammation leads to synovial lining hyperplasia and the formation of pannus, a thickened cellular membrane of granulation–reactive fibrovascular tissue that invades the underlying cartilage and bone[5].

CLINICAL FEATURES

Patients often complain of early morning joint stiffness lasting more than 1 hour and easing with physical activity. The earliest involved joints are typically the small joints of the hands and feet. The initial pattern of joint involvement may be monoarticular, oligoarticular (<4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with an inflammatory arthritis will present with too few affected joints and other characteristic features to be classified as having RA—so-called undifferentiated inflammatory arthritis.

Once the disease process of RA is established, the wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) are the most frequently involved joints. Flexor tendon tenosynovitis is a frequent hallmark of RA. Ulnar deviation results from subluxation of the MCP joints and proximal phalanx. Hyperextension of the PIP joint with flexion of the DIP joint ("swan-neck deformity"), flexion of the PIP joint with hyperextension of the DIP joint ("boutonnière deformity"), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint ("Z-line deformity") also may result from damage to the tendons, joint

capsule, and other soft tissues in these small joints. Atlantoaxial-subluxation is clinically noteworthy because of its potential to cause compressive myelopathy.

EXTRAARTICULAR MANIFESTATIONS

Extraarticular manifestations may develop at any time during the clinical course of RA, sometimes even prior to the onset of arthritis. Constitutional symptoms include weight loss, fever, fatigue, malaise and depression.

ORGAN SYSTEM	**INVOLVEMENT**
Skin	Rheumatoid nodules, vasculitis
Ocular	Keratoconjunctivitis sicca, iritis, Episcleritis
Oral	Salivary inflammation (sicca symptoms)
Respiratory	Pulmonary fibrosis, pleural effusion, cricoarytenoid inflammation
Cardiac	Pericardial inflammation, valvular nodule formation, myocarditis
Renal	Proliferative glomerulonephritis, membranous nephropathy, amyloidosis
Neurological	Mononeuritis, nerve entrapment, cervical Instability
Hepatic	Increased aminotransferase concentrations
Haematological	Anaemia, thrombocytosis, leucocytosis, lymphadenopathy Felty's syndrome: splenomegaly, Thrombocytopenia
Vascular	Vasculitis

Table-1: Extraarticular manifestations in Rheumatoid Arthritis

LABORATORY FINDINGS

Like any other autoimmune disease, there is no specific test to diagnose RA with certainty. Rheumatoid factors (RF) are autoantibodies reactive against the Fc portion of IgG. These autoantibodies are usually of IgM in nature. Rheumatoid factors are usually detected in more than two-thirds of adults and have been used to evaluate patients with RA. However, RF is not specific for RA as it is found in 5% of normal adults. The prevalence of RF increases with age and has been found in 10 to 20% of individuals more than 65 years of age. Other disease conditions associated with positive RF includes systemic lupus erythematosus, Sjögren's syndrome, interstitial pulmonary fibrosis, sarcoidosis, hepatitis B, chronic liver disease, infectious mononucleosis, tuberculosis, leprosy, syphilis, subacute bacterial endocarditis, visceral leishmaniasis, schistosomiasis and malaria. It may also appear transiently in normal individuals after vaccination or transfusion. The presence of rheumatoid factor does not establish the diagnosis of RA. However, the presence of RF can be of prognostic significance because patients with high titers tend to have more severe and progressive disease with extraarticular manifestations. RF is uniformly found in patients with nodules or vasculitis.

Other serologic test used to evaluate patients with RA is antibodies to cyclic citrullinated peptides (anti-CCP). These antibodies are usually found in rheumatoid factor–positive patients, on occasion they can be detected in the absence of rheumatoid factor as well. The anti-CCP test has a similar sensitivity and a better specificity for RA than does rheumatoid factor. In individuals with early RA, assessment of anti-CCP may be the most useful to confirm the diagnosis. Anti-CCP's most commonly occurs in persons with aggressive disease with a tendency for developing bone erosions, in those who smoke cigarettes and in those who are

associated with HLA beta-1 allele. it is a useful test to confirm a diagnosis of RA and to estimate prognosis.

Normochromic, normocytic anemia is frequently present in active RA. It is due to ineffective erythropoiesis. Anemia and thrombocytosis correlate with disease activity. The white blood cell count is usually normal, but a mild leukocytosis can occur. Eosinophilia, when present, usually reflects severe systemic disease. The erythrocyte sedimentation rate (ESR) is increased in nearly all patients with active RA. Other acute-phase reactants including ceruloplasmin and C-reactive protein are also elevated, and generally such elevations correlate with disease activity and predict progressive joint damage.

The synovial fluid is usually turbid, with reduced viscosity. Its protein content is increased and glucose concentration is slightly decreased or normal. The white cell count varies between 5 and 50,000/ μL and polymorphs predominate. Complements C3 and C4 are markedly diminished in synovial fluid as a result of activation of the classic complement pathway by locally produced immune complexes.

RADIOGRAPHIC EVALUATION

Early in the course of the disease radiographic evaluation reveals only soft tissue swelling and joint effusion. Juxtaarticular osteopenia, loss of articular cartilage and bone erosions develop after months of sustained activity. The primary value of radiography is to determine the extent of cartilage destruction and bone erosion and for monitoring the impact of therapy.

DIAGNOSIS

The diagnosis of RA can be delayed due to the nonspecific nature of initial symptoms. A period of obse rvation may be necessary before the diagnosis can be established. A definitive diagnosis of RA depends mainly on the characteristic clinical features along with exclusion of other inflammatory processes. The isolated finding of a positive rheumatoid factor, anti-CCP antibody, or an elevated ESR or CRP should not itself be used as evidence of RA.

The American College of Rheumatology developed revised criteria for the classification of RA in 1987. These criteria have a sensitivity of 91–94% and a specificity of 89% when used to classify patients with RA. Although these criteria were developed for investigational purposes, they can be used for establishing the diagnosis as well. Failure to meet these criteria does not exclude the diagnosis.

ACR Revised Criteria for the Classification of RA (1987)[6]:

1. Guidelines for classification
    a. Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA).
    b. b. Patients with two or more clinical diagnoses are not excluded
2. Criteria[a]
    a. Morning stiffness: Stiffness in and around the joints lasting 1 h before maximal improvement.

b. Arthritis of three or more joint areas: At least three joint areas, observed by a physician simultaneously, have soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints.

c. Arthritis of hand joints: Arthritis of wrist, metacarpophalangeal joint, or proximal interphalangeal joint.

d. Symmetric arthritis: Simultaneous involvement of the same joint areas on both sides of the body.

e. Rheumatoid nodules: Subcutaneous nodules over bony prominences, extensor surfaces, or juxtaarticular regions observed by a physician.

f. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects

g. Radiographic changes: Typical changes of RA on posteroanterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

[a]Criteria a–d must be present for at least 6 weeks. Criteria b–e must be observed by a physician.

RENAL INVOLVEMENT IN RHEUMATOID ARTHRITIS

Renal involvement is generally considered to be quite rare, although RA is often characterized by the presence of rheumatoid factors and circulating immune complexes[7].

Population-based studies have proven that patients with RA have an increased mortality relative to age-matched controls, and that this increased mortality has been attributed to renal disease[8,9].

Renal involvement in RA has been broadly classified into two broad categories: lesions caused by the disease itself and lesions occurring as a result of drugs used in the management of disease.

Renal involvement in rheumatoid arthritis (RA):

- Renal disorders related to RA:

  Amyloidosis

  Glomerular lesions

  Vascular lesions

  Tubulointerstitial lesions

- Renal disorders related to drug therapy:

  Nonsteroidal antiinflammatory drugs

  Analgesics

  Gold/penicillamine

  Cyclosporine

Prevalence and patterns of renal disease in rheumatoid arthritis:

The prevalence of renal disease in rheumatoid arthritis has been examined using three types of study, based either on death certificates or on autopsy studies or renal biopsy studies. Interpretation of these studies is complicated by differences in the definitions of rheumatoid arthritis, the duration of disease at death, the treatment received, the accuracy of death certification, and the method of statistical analysis.

Incidence of renal disease in rheumatoid arthritis: Death certificate studies:

Study	Country	Number of patients	Renal amyloid (%)	Renal failure (%)
Cobb *et al.* (1953)[10]	USA	130	3.1	10
Rasker and Cosh (1981)[11]	UK	43	7	11.6
Prior *et al.* (1984)[12]	UK	199	1.5	3.0
Laasko *et al.* (1986)[9]	Finland	356	8.7	11.8

Autopsy studies in rheumatoid arthritis:

Study	Country	Number of patients	Renal amyloid (%)	Renal failure (%)
Missen and Taylor (1956)[13]	UK	47	17	-
Mutru *et al.* (1976)[14]	Finland	41	17	27
Ramirez *et al.* (1981)[15]	USA	76	8	9
Boers *et al.* (1987)[16]	Holland	132	11	23
Suzuki *et al.* (1994)[17]	Japan	81	21	9.9

In autopsy studies the proportion of patients with renal failure ranged from 9 to 27 per cent, and of renal amyloid from 8 to 17 per cent. The high prevalence of renal failure in the autopsy studies is at variance with clinical experience. In addition to renal amyloid, autopsy studies in the

1940s showed a proliferative glomerulonephritis. Some studies have shown a high incidence of glomerulonephritis and renal vasculitis.

Renal biopsy studies in rheumatoid arthritis:

Study	Number of patients	Clinical features	Normal	Mesangial proliferative	Membra-nous	Amyloid	Tubulo-interstitial nephritis	Others
Brun *et al.* (1965)[18]	32	Normal, proteinuria, renal impairment	11	0	1	4	9	7
Salomon *et al.* (1974)[19]	18	Normal, proteinuria, microscopic haematuria	11	7	0	0	0	0
Orjavik *et al.* (1981)[20]	14	Proteinuria, nephrotic syndrome	0	5	0	7	0	2
Sellars *et al.* (1983)[21]	30	Proteinuria, microscopic haematuria, nephrotic syndrome	0	13	9	1	4	3
Hordon *et al.* (1984)[22]	21	Microscopic haematuria	1	15	1	0	1	3
Helin *et al.* (1986)[23]	39	Proteinuria, nephrotic syndrome, renal impairment	3	11	9	16	0	0
Adu *et al.* (1993)[24]	90	Proteinuria, nephrotic syndrome, renal impairment	0	10	18	13	14	35
Korpela *et al.* (1990)[25]	74	Not given	7	23	13	20	3	8
Nakano *et al.* (1998)[26]	158	Proteinuria, nephrotic syndrome haematuria, renal impairment	20	54	49	30	-	5

Renal biopsy studies have not provided evidence of a consistent pattern of renal disease. Most of the earlier studies included patients with minor urinary abnormalities and this explains the lesser incidence of glomerular diseases and more normal biopsies. The studies by Brun et al[18] and Saloman et al[19] nhad 11 normal biopsies each. Further studies identified the renal involvement secondary to drugs like gold and penicillamine. Later studies proved that glomerular diseases can also occur in patients who have not received gold or penicillamine.

AMYLOIDOSIS

Amyloidosis is a systemic disease characterized by deposition of an insoluble proteinaceous material in the extracellular matrix of multiple organs. These proteinaceous deposits have a unique fibrillar ultrastructure characterized by a rigid, nonbranching filament of about 100 Å in diameter. Amyloidosis is classified according to the type of fibril deposited –AA amyloidosis (secondary amyloidosis) which occurs as a result of chronic inflammatory response and AL amyloidosis (primary amyloidosis) which is usually associated with plasma cell dyscrasias.

Rheumatoid arthritis and juvenile chronic arthritis are the most common causes of AA amyloidosis in developed countries. Rheumatoid arthritis-associated AA amyloid is more common in Europe and Japan. There has been a decline in prevalence of RA associated amyloid in the last 20 years, particularly more so in the last 5 years. The reason for this declining trend could be attributed to much more aggressive therapy which reduces the persistently elevated

acute phase response. Proteinuria, often with a nephrotic syndrome, is the most common clinical presentation. Other presentation includes either acute or chronic kidney disease.

PATHOLOGY OF AMYLOIDOSIS:

The diagnosis of amyloid in RA is based on histological examination of rectal biopsy or abdominal fat pad biopsy. In patients with renal abnormalities a renal biopsy is indicated. Renal biopsy reveals an amorphous acellular material that is periodic-acid Schiff negative. When stained with congo red stain and examined under polarized light, a characteristic apple green birefringence is noted. Congo red staining in AA amyloid is sensitive to potassium permanganate unlike AL amyloid which is resistant. Immunohistochemistry using antibodies to immunoglobulin light chains may also confirm AL amyloid.

CLINICAL COURSE AND TREATMENT OF AMYLOIDOSIS

Amyloidosis is usually seen in with patients with long-standing RA (>10 years duration) and is also more common in patients who are positive for rheumatoid factor (RF) and who have significant joint destruction. The clinical course of AA amyloidosis in patients with RA is usually progressive, as there are no satisfactory treatments aside from aggressive treatment of the underlying disorder. In a randomized controlled trial, Ahlmen et al[27] reported a 5-year patient survival of 89 per cent in patients who received cytotoxics as compared to 29 per cent in untreated patients. Elkayam et al reported resolution of proteinuria and stabilization of amyloid deposits by serial ^{123}I-labeled serum amyloid P scintigraphy in a woman with rheumatoid arthritis of 10 years duration and proteinuria (900 mg per 24 hours) treated with infliximab.[28] It is now evident that aggressive management of active joint inflammation may decrease the frequency and severity of AA amyloidosis in patients with RA. Poor prognostic factors include

cardiac involvement and serum creatinine level greater than 2.0 mg/dL at presentation.[29] Also patients with amyloidosis generally do poorly on dialysis, and recurrence of amyloid deposits has been reported in transplanted kidneys.[30]

PROLIFERATIVE GLOMERULONEPHRITIS

Focal or diffuse endocapillary proliferative glomerulonephritis is rare in rheumatoid arthritis. In the study by Boers et al,[16] only 5 of 132 cases had a proliferative glomerulonephritis (diffuse in one and focal in four). Davis et al[31] reported a case of proliferative glomerulonephritis in whom the renal biopsy showed mesangial hypercellularity and proliferative changes in the glomeruli, and electron microscopy revealed subendothelial deposits. Ramirez et al[15] identified 3 cases of proliferative glomerulonephritis in 76 renal biopsies. Helin et al[32] reported 4 cases of proliferative glomerulonephritis out of 110 biopsies. Despite the presence of circulating immune complexes, proliferative glomerulonephritis is not seen commonly in RA. It is considered that the circulating immune complexes in RA might have reduced complement fixing ability.

MESANGIAL PROLIFERATIVE GLOMERULOPATHY

Several studies in patients with RA and microscopic haematuria have reported a mild mesangial proliferative glomerulonephritis. Mesangial proliferation is the most common renal lesion identified in patients with RA.[19,21,22,25,26] This lesion is characterized by increased mesangial matrix and hypercellularity and mesangial deposits of IgM, IgA, and C3.[33] Forty out of 110 patients in the study by Helin et al[32] and 54 out of 158 by Nakano et al[26] had mesangial proliferation. Despite the findings of glomerulitis on renal biopsy, the clinical consequences of these lesions are minor. The most frequent manifestations of mesangial proliferative

glomerulopathy in RA are microscopic hematuria and low-grade proteinuria. Follow-up of these patients has shown a benign course and progression to renal insufficiency and/or increasing of proteinuria is very rare[32].

IGA NEPHROPATHY

In the studies of Sellars et al[21], Helin et al[23], and Korpela et al[25], several patients described with a mesangial proliferative glomerulonephritis had mesangial IgA deposits. In a Japanese study, Nakano et al[26] reported a very high incidence of IgA nephropathy, with 26 out of 158 patients who underwent biopsies revealed mesangial IgA deposits. As in idiopathic IgA nephropathy, the pathogenetic mechanisms of this disorder in patients with RA are unclear. To clarify the pathogenesis of IgA glomerulopathy in patients with RA, Nakano et al[34] examined class specific rheumatoid factors, including IgA-RF. There was little correlation between histopathological findings and the serum concentration of any class of RF, although the mean IgA-RF concentration was slightly higher in patients wth IgA glomerulopathy than in the group with non-IgA glomerular diseases. Certain genetic or geographic factors have also been related to the onset of primary IgA nephropathy. A significant association has been identified between HLA-DR4 and primary IgA nephropathy[35]. HLA-DR4 antigen is also thought to be related to the occurrence and progression of RA[36]. Therefore, a common pathogenetic basis may exist that explains the ocurrence of RA and IgA nephropathy. However, because IgA nephropathy is the most common primary glomerular disease in the Japanese population, the prevalence of IgA nephropathy in RA in the study by Nakano et al[26] may be related to the high frequency of IgA glomerulopathy in the Japanese population. The results of this study should be interpreted with caution when applying to the general population.

MEMBRANOUS NEPHROPATHY

The most common cause of membranous nephropathy in patients with rheumatoid arthritis is gold or penicillamine therapy. However, there are now many reports of such patients who had never been on gold or penicillamine, and who have a membranous nephropathy unrelated to drug treatment. The numbers of reported cases make it unlikely that this association is coincidental. Honkanen et al[37] reported on four patients with rheumatoid arthritis and membranous nephropathy, and reviewed the literature. Only one of their four patients had received gold and that was 16 years before the renal biopsy. Adu et al[24] observed six patients with rheumatoid arthritis and membranous nephropathy, none of whom had been treated with penicillamine, although two had received gold that was discontinued 17 and 13 years before renal biopsy. Membranous nephropathy in the setting of an auto-immune disease might be secondary to systemic lupus erythematosus(SLE), hence it seems prudent to rule out SLE in RA associated membranous nephropathy. None of the patients in the reports by Honkanen et al and Adu et al, had clinical or serological evidence of SLE.

GLOMERULAR BASEMENT MEMBRANE IN RA

Saito et al[38] reported a study on the thickness of glomerular basement membrane. He compared thickness of the glomerular basement membrane in 48 RA patients as against 10 controls after ruling out hereditary thin basement membrane disease and secondary glomerular diseases. The mean GBM thickness was found to be significantly thinner in RA patients as against the control group. However, the authors found that the mean GBM thickness of RA patients without gold sodium thiomalate treatment (GST) was not statistically different from the control group, while RA patients who received GST had significantly thinner GBM as compared

to controls. This led the authors to conclude that the thinning of GBM in RA may be related to GST treatment.

VASCULITIS IN RA

The clinical spectrum of rheumatoid arthritis includes a systemic vasculitis, with involvement of blood vessels ranging in size from capillaries to small- and medium-sized arteries. The clinical presentation includes nailfold infarcts, a leucocytoclastic vasculitis, a peripheral neuropathy, pericarditis, gastrointestinal infarcts, and renal vasculitis. Data registry from Norwich Health Authority in the United Kingdom suggests an annual incidence of systemic rheumatoid vasculitis of 12.5 per million population[39].

Pathogenesis

The pathogenesis of vasculitic glomerulonephritis in rheumatoid arthritis is unknown. The majority of renal biopsies in the patients with this lesion show no significant immune deposits[40]. This pauci-immune vasculitic glomerulonephritis is similar to that seen in microscopic polyangiitis and Wegener's granulomatosis. Several patients with rheumatoid arthritis and a vasculitic glomerulonephritis have had antineutrophil cytoplasmic antibodies (ANCA) and in some studies these were directed against myeloperoxidase[41]. It is, however, difficult to establish a pathogenic role for ANCA in rheumatoid vasculitis. The prevalence of ANCA positivity in RA patients varies from 20 -40 per cent[42,43]. Coremans et al, reported antilactoferrin antibodies in patients with RA associated vasculitis[44].

Pathology

In an autopsy study by Boers et al,[16] of 132 patients with rheumatoid disease found a large vessel renal vasculitis in 8 of 18 cases with systemic vasculitis, and in four patients there was an extracapillary proliferative glomerulonephritis. There are now several case reports and small

series of necrotizing and crescentic glomerulonephritis in patients with rheumatoid arthritis (Breedveld et al. 1985; Kuznetsky et al. 1986; Harper et al. 1997; Messiaen et al. 1998; Yorioka et al. 1999; Qarni and Kohan 2000). The renal pathology is of a vasculitic glomerulonephritis with focal and segmental necrosis of glomerular capillaries, breaks in the capillary walls, and extracapillary proliferation with a crescentic glomerulonephritis (Kuznetsky et al. 1986; Harper et al. 1997; Messiaen et al. 1998) (Fig. 2). Only 23 per cent of renal biopsies show significant glomerular immune deposits. An extraglomerular renal vasculitis is found in only 12 per cent of cases. Occasional patients may have other glomerular lesions such as a membranous nephropathy (Kuznetsky et al. 1986; Harper et al. 1997) or amyloidosis (Kiyama et al. 1991; Harper et al. 1997). Similar glomerular lesions have also been reported in patients with rheumatoid arthritis and other disorders who were treated with penicillamine.

Clinical presentation

The median age at onset from the published studies was 62 years with a range of 22â€“76 years and the median duration of rheumatoid arthritis of 13 years (range 1â€“40 years). Both genders are equally affected. Eighty-five per cent of patients are seropositive and 50 per cent of patients have extrarenal vasculitis. The clinical presentation is with microscopic haematuria and proteinuria in 90 per cent of cases and all patients have renal impairment or renal failure, which may be severe enough to require dialysis.

Treatment and outcome

Treatment is with prednisolone and cyclophosphamide in the doses used to treat microscopic polyangiitis (see Chapter 4.5.3). The prognosis is reasonable with 95 per cent of patients surviving the acute illness. However, renal failure may be irreversible and require long-term dialysis. These studies show that, in addition to a renal arteritis, patients with rheumatoid arthritis

may develop a vasculitic glomerulonephritis that by light microscopy appears similar to that seen in microscopic polyarteritis and Wegener's granulomatosis.

RENAL DISEASES RELATED TO DRUG THERAPY

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Nonsteroidal antiinflammatory drugs (NSAIDs) remain the backbone of rheumatoid arthritis therapy. Their anti-inflammatory effect is mediated by inhibition of cyclooxygenase, which is involved in synthesis of prostaglandins. Inhibition of renal prostaglandin synthesis results in reduced glomerular blood flow[57,58]. In addition to this hemodynamically mediated action, NSAIDs can also cause interstitial nephritis. Interstitial nephritis is usually reversible and recovery occurs when the drugs are discontinued. The selective cyclooxygenase-2 inhibitors also have the same adverse effects on renal function, as do other NSAIDs. When a patient with RA presents with evidence of decreased renal function or interstitial changes, discontinuation of NSAIDs should be the first step taken in the management protocol. Analgesic nephropathy is a combination of papillary necrosis and interstitial nephritis. It usually occurred with phenacetin. It can also occur with ibuprofen, phenylbutazone, naproxen, and mefenamic acid particularly when used in combination.

RENAL LESIONS ASSOCIATED WITH GOLD THERAPY

The use of gold salts in the treatment of RA was first described by Forestier in 1935. With the availability of newer agents, gold treatment is used less often now. The hallmark of renal toxicity from gold is proteinuria, occurring in 3% to 10% of RA patients. Proteinuria usually occurs 4 to 6 months after the initiation of gold therapy. The severity of proteinuria is

usually not proportional to the dose of gold received. The proteinuria resolves gradually with discontinuation of gold[59], steroids were not required. The renal histology associated with gold-induced proteinuria is membranous glomerulopathy. Light microscopy shows uniform basement membrane thickening, and electron microscopy shows subepithelial deposits. Gold-induced proteinuria is common in patients with the HLA antigens B8 and DR3[60].

RENAL LESIONS ASSOCIATED WITH PENICILLAMINE THERAPY

Penicillamine was introduced in the 1950s for the treatment of Wilson's disease. Later it has been tried in RA and used widely until methotrexate became available. It is a slow-acting drug and usually takes 3 to 6 months for responses to occur. Penicillamine induced nephropathy is similar to gold nephropathy and causes hematuria and/or proteinuria. Because it is a slowly acting drug, the onset of proteinuria is also delayed with an average of 8 months of initiation of therapy. After the discontinuation of penicillamine, proteinuria resolves spontaneously. No steroid therapy is warranted as spontaneous remission is the rule[61]. Histologically, penicillamine-induced renal lesions manifests as membranous nephropathy. Apart from causing membranous nephropathy, penicillamine causes a wide variety of renal lesions. It induces antibodies to histones to result in drug induced lupus, it also triggers anti neutrophilic cytoplasmic antibodies to result in vasculitis that may even present as rapidly progressive crescentic glomerulonephritis[62]. Penicillamine-induced crescentic glomerulonephritis requires aggressive immunosuppressive therapy. Clinical picture of Goodpasture's syndrome has also been reported following penicillamine therapy[63].

RENAL LESIONS ASSOCIATED WITH METHOTREXATE AND OTHER DMARD THERAPY

Methotrexate is a folic acid antagonist and is one of the major DMARD used in the treatment of RA. Methotrexate when used in high doses in the treatment of malignancies has been associated with renal failure. But renal failure is extremely rare, when methotrexate is used in low doses (5 to 25 mg/week) to treat RA. On the other hand, renal failure can significantly alter the metabolism of methotrexate and increase its toxicity[64]. Hence methotrexate needs dose reduction in renal failure and better avoided in severe renal dysfunction. Renal function has to be monitored regularly in those patients taking methotrexate and having mild renal insufficiency. Other commonly used DMARDs such as hydroxychloroquine, azathioprine, leflunomide, sulfasalazine and the newer biologic agents like etanercept and infliximab does not have nephrotoxicity[65].

MATERIALS AND METHODS

Study centre : Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai.

Study Design : Prospective observational study.

Study period : September 2010 to February 2013.

INCLUSION CRITERIA:

1. Rheumatoid arthritis was diagnosed by rheumatologist and all the patients fulfilled the American College of Rheumatology Revised Criteria for the Classification of RA (1987)[6].
2. All Rheumatoid Arthritis patients attending rheumatology clinic were considered for screening and those patients who had abnormal urine sediments (RBC's, RBC Cast) or proteinuria (>0.3gm/day) or raised serum creatinine (>1.2mg/dl) will be included in the study.
3. Patients who were both sero-positive and sero-negative for rheumatoid factor were included.
4. Apart from screening, those patients who have been referred from rheumatology department for abnormal urine sediments or raised serum creatinine were also included.

EXCLUSION CRITERIA:

1. Patients who had normal urine analysis and normal serum creatinine were excluded from the study.

2. Rheumatoid Arthritis patients with diabetes mellitus, hepatitis B and C, human immunodeficiency virus, syphilis and other diseases known to cause glomerular pathology were excluded from the study.

METHODS

All rheumatoid arthritis patients were subjected to screening tests which included urine analysis and blood urea and serum creatinine estimation. Urine analysis, blood urea and serum creatinine estimation were done at renal lab, department of nephrology.

1. HISTORY

Age and sex of the patient was noted. Duration of rheumatoid arthritis, drug history with special interest to duration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), methotrexate and other Disease Modifying Anti-Rheumatic Drugs(DMARDs) were noted. Consumption of indigenous medicines was also probed. Symptoms of joint pain, joint swelling, edema legs, oliguria and hematuria were noted. History of hypertension was also noted.

2. EXAMINATION

Height and weight of the patient was recorded. Blood pressure was recorded thrice and the average taken. Presence of joint swelling, tenderness and deformities were noted. General examination was made with special interest to lymphadenopathy, subcutaneous nodules and purpuric spots over extremities or vasculitic ulcers. Complete systemic examination were done.

3. URINE ANALYSIS

Microhematuria is defined as more than or equal to 5 RBC's per high power field. Proteinuria is quantified by spot urine protein to creatinine ratio (PCR). Nephrotic syndrome is defined as urine PCR more than 3.5. Sub-Nephrotic proteinuria is used when urine PCR is

between 1 and 3.5. Those with urine PCR between 0.3 and 1 were also included in the study to assess the clinic-pathologic correlation. Urine culture was also done for all patients.

4. BLOOD INVESTIGATIONS

Complete hemogram including hemoglobin, total and differential WBC count, Erythrocyte Sedimentation Rate (ESR) and platelet count were done. Random blood sugar was done in all cases and fasting and post-prandial blood sugar was done when appropriate. Blood urea, serum creatinine and electrolytes, serum complements C3 and C4 were also done.

5. RHEUMATOID FACTOR AND C-REACTIVE PROTEIN

Rheumatoid factor (RF) and C- Reactive Protein (CRP) was done in rheumatology lab. Rheumatoid factor was done by latex agglutination method and a value of more than 8 IU/ml was considered positive. The test will be repeated in higher titres and the maximum titre is given as more than 256 IU/ml. CRP was done by nephelometry and values are expressed in mg/L. CRP of more than 6 mg/L was considered positive. Antibodies to cyclic citrullinated peptides (anti-CCP) was done only in selected patients to confirm the diagnosis. It was done by ELISA and values more than 6.5 IU/ml is considered positive.

6. RADIOLOGIC INVESTIGATIONS

Chest X-ray was taken for all patients. Ultrasonogram of the kidney, ureter and bladder was done with full bladder in all patients. Kidney size, echoes, cortico-medullary differentiation and pelvi-calyceal system were noted.

After getting the Ultrasonogram, those with normal sized kidneys with urinary abnormalities and/or raised serum creatinine were subjected for renal biopsy. Those with kidneys of size less than 8 cm or those with grade III increased echoes and poor cortico-medullary

differentiation with raised serum creatinine were labeled as chronic kidney disease at entry into study and biopsy was deferred in this group.

7. RENAL BIOPSY

After getting informed consent for percutaneous renal biopsy, bleeding time, clotting time, prothrombin time, International Normalised ratio (INR) were done to ensure normal bleeding and clotting profile. The position and depth of the left kidney was marked with bed side Ultrasonogram. After ensuring strict asepsis, under local anaesthesia, percutaneous renal biopsy was done using 18G automatic spring loaded biopsy gun (BARD biopsy gun). Two tissues were taken. One is preserved in formalin for light microscopy and the other in Michel's fixative for immunoflourescence study. In light microscopy, sections are studied with Hematoxylin and eosin, Per-iodic acid Schiff and Masson's trichrome stain for all specimens. Silver, congo red and other special stains were applied as appropriate. Immunofluorescence was studied for IgA, IgM, IgG, C3, C1q and for kappa (κ) and lambda (λ) light chains. Immunohistochemistry was also used in special circumstances like detection of AA in case of amyloidosis. Post biopsy patient was observed for hematuria, hypotension and loin pain.

FOLLOW UP

The patients were followed up for 3 to 28 months (mean 15 months). All Patients were followed up every 2 weeks. At follow up, urine analysis, urine PCR, hemogram and serum creatinine was done in all cases. For those who had proteinuria at presentation, the following definitions were used at follow up.

Complete remission: urine spot protein- creatinine ratio less than 0.3

Partial remission: urine spot protein- creatinine ratio less than 1 or 50% reduction from baseline value during follow up.

ESTIMATED GLOMERULAR FILTRATION RATE

Estimated glomerular filtration rate (eGFR) was calculated using CockCroft-Gault equation:

$$\text{Estimated Creatinine clearance(ml/min)} = \frac{(140 - \text{age}) \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg / dl)}}$$

This equation is for men. It is multiplied by 0.85 for women.

STATISTICAL ANALYSIS

Statistical analyses were done using Graphpad software. Patient demographics were presented as mean, median and range. Univariate analyses were done by Fisher's exact test and two tailed Student's *t* test and p-value less than 0.05 were considered significant.

RESULTS

The study population included patients referred to the department of nephrology as well as patients who were screened at the department of Rheumatology. Total number of patients screened was 300. Out of this 300 patients, 27 were asymptomatic and was detected to have either urinary abnormalities or raised serum creatinine without urinary abnormalities only on screening. About 25 patients were symptomatic and had been referred to the department of nephrology for urinary abnormalities or raised serum creatinine or both. Hence total number of patients included for final analysis was 52, of which females were 31 as shown in table – 1.

TABLE – 1	
TOTAL NUMBER OF PATIENTS INCLUDED IN THE STUDY	**52**
FEMALE : MALE	**1.5 : 1**

AGE DISTRIBUTION:

The age distribution ranged from 18 to 67 years, with mean $\pm$ SD being 45.17 $\pm$ 11.7 years. Most of the individuals were in the third and fourth decade.

TABLE – 2	
AGE GROUP	**N**
Less than20	1
21 – 30	5
31 – 40	13
41 – 50	16
51 – 60	12
More than 60	5
Total	**52**

PATIENT CHARACTERISTICS:

The duration of illness in our patients at the entry of study varied from 6 months to 30 years, with the mean of 8.5 years. About 80 percent of them had positive rheumatoid factor (RF). Hypertension was noted in 11 patients (21.2%) as shown in table – 3. Extra-renal symptoms and signs and joint deformities are summarized in tables 4 and 5 respectively.

TABLE – 3	
Mean duration of RA (years)	8.5
Rheumatoid factor positivity –N(%)	42 (80.7%)
Mean ESR (mm in 1st Hr)	54.8
Mean CRP (mg/L)	10.6
Hypertension - N(%)	11 (21.2%)
Diabetes mellitus- N	0

TABLE – 4 : EXTRA-RENAL SYMPTOMS/SIGNS:	
FEATURES	N(%)
1.Joint pain	47 (90.3%)
2.Early morning stiffness	50 (96%)
3.Fever	6 (11.5%)
4.Subcutaneous nodules	9 (17.3%)
5. Joint deformities	28 (53.8%)

TABLE – 5 : JOINT DEFORMITIES	
Hallux valgus	1
Swan-neck deformity	2
Boutonniere deformity	2
Ulnar deviation of hand	2
Multiple small joint arthritis of hand	21

TREATMENT HISTORY:

Almost all patients except two were on steroid therapy at the entry of study. Two patients had joint pain and early morning stiffness for more than 6 months, but presented with nephritic syndrome. They were diagnosed to have rheumatoid arthritis during the evaluation of renal disease. Hence they were not on steroids and NSAIDS at diagnosis of renal disease. All other patients were on tablet prednisolone 5 to 10 mg per day. Except these two patients all other patients were on NSAIDS as well, until they were diagnosed to have renal disease. The most commonly used NSAID was tablet Indomethacin 2 to 3 mg per Kg per day. About 23 patients were on Methotrexate therapy. The dose of Methotrexate ranged from 7.5 mg to 20 mg per week. Hydroxychloroquine was used in 18 patients, while 9 patients received a combination of Hydroxychloroquine and Methotrexate.

TABLE – 6	
Pt's receiving prednisolone N(%)	50 (96%)
-Dose in mg/day (median)	10
Pt's receiving Methotrexate N(%)	23 (44.2%)
-Dose in mg/week (median)	7.5
Pt's receiving Hydroxychloroquine N(%)	18 (35%)
-Dose in mg/ day (median)	200

CLINICAL PRESENTATION:

The common symptom at presentation was edema of the legs followed by hypertension and oliguria. Two patients presented with macrohematuria. About 27 patients did not have any renal symptoms and was detected to have either urinary abnormalities or raised serum creatinine only by screening. The clinical presentation is summarized in table – 7.

TABLE – 7	
Clinical feature	**N(%)**
Edema	15 (28.8%)
Oliguria	7 (13.4%)
Macrohematuria	2 (3.8%)
Asymptomatic	27 (51.9%)

The various renal syndromes with which the patients presented is depicted in table -8

TABLE – 8	
RENAL SYNDROME	**N(%)**
Nephrotic syndrome	8 (13.4%)
Nephritic syndrome	4 (7.6%)
Asymptomatic urinary abnormalities	12 (23%)
Acute kidney injury	2 (3.8%)
Hypertension	11 (21.2%)
Chronic kidney disease	23 (44.2%)

The proportion of patients with urinary abnormalities including proteinuria, microhematuria and renal failure at presentation is classified in table – 9.

TABLE – 9	
FEATURE	**N (%)**
Microhematuria	4 (7.6%)
Nephrotic range proteinuria without renal dysfunction	5 (9.6%)
Nephrotic range proteinuria with renal dysfunction	3 (5.8%)
Proteinuria (sub-nephrotic) without renal dysfunction	13 (25%)
Proteinuria (sub-nephrotic) with renal dysfunction	2 (3.8%)
Renal failure without urinary abnormalities	23 (44.2%)

RENAL BIOPSY:

At entry into study, about 23 patients (44%) had evidence of chronic kidney disease in the form of raised serum creatinine with Ultrasonogram showing reduced kidney size with grade III echoes or poor cortico- medullary junction. Rest of the patients(n=29) had normal sized kidneys and presented with proteinuria and/or nephritic syndrome or acute kidney injury. All of these 29 patients underwent renal biopsy. The two patients who had acute kidney injury had acute interstitial nephritis and acute tubular necrosis. The remainder of patients had glomerular diseases identified in biopsy. The most common lesion noted was mesangial proliferative glomerulopathy, followed by focal endocapillary proliferative glomerulonephritis.

TABLE – 10	
Renal histology	**N**
1.Mesangial proliferative glomerulopathy	9
2.Focal endocapillary proliferative glomerulonephritis	5
3.IgA nephropathy	3
4.Minimal change disease	2
5.Membranous nephropathy	2
6.Amyloidosis	2
7.Focal segmental glomerulosclerosis	2
8. Nodular glomerulosclerosis	1
9.Ischemic glomerulosclerosis	1
10. Acute interstitial nephritis	1
11.Acute tubular injury	1
12.Total	29

TUBULO-INTERSTITIUM AND VASCULAR COMPARTMENT:

Tubulo-interstitium was normal in 19 cases. The renal biopsy in the two cases of acute kidney injury showed lymphocytic infiltrates suggestive of acute interstitial nephritis in one and acute tubular injury (previously acute tubular necrosis) in the other. Interstitial fibrosis with tubular atrophy (varied from 10 to 50%) was noted in 3 cases. Blood vessels were thickened in 7 patients out of which only 1 had hypertension. The remaining 6 patients had vascular changes in the absence of hypertension. Fibro-intimal proliferation of blood vessels were seen in 2 cases.

IMMUNOFLUORESCENCE MICROSCOPY:

Dominant or Co-dominant mesangial deposits of IgA were found in 3 cases. The immunoflourescence pattern in other glomerular diseases is shown in table-11.

TABLE – 11

GLOMERULAR DISEASE	**IMMUNOFLUORESCENCE PATTERN (IF)**	**No. of cases**
Mesangial proliferative glomerulopathy (n= 9)	IgM and C3	5
	IgM, C3 and C1q	1
	IgM alone	1
	IgG alone	1
	C3 alone	1
Focal endocapillary proliferative glomerulonephritis (n= 5)	IgG and C3	2
	IgG, IgA and C3	1
	IgM and C3	1
	C3 alone	1
Membranous nephropathy (n= 2)	IgG and C3	1
	IgG, IgM and C3	1
Focal segmental glomerulosclerosis (n=2)	IgM and C3	1
	IgM alone	1
Ischemic glomerulosclerosis (n =1)	C3 alone	1
Amyloidosis (n=2) Minimal change disease (n= 2) Nodular glomerulosclerosis (n = 1)	No IF deposits	

RENAL HISTOPATHOLOGY AND CLINICAL PRESENTATION

Among 29 patients who underwent biopsy, 8 presented with oedema legs and had nephrotic range proteinuria. Out of these 8 patients, 3 had evidence of renal dysfunction (eGFR < 60 ml/mt) at presentation. The histopathology in the cohort of nephrotic syndrome included, membranous nephropathy, amyloidosis and focal segmental glomerulosclerosis – 2 cases each, followed by minimal change disease and nodular glomerulosclerosis - 1 case each. The histopathology in nephritic syndrome was consistent with focal proliferative glomerulonephritis in 3 cases and IgA nephropathy in 1 case. About 12 patients did not have edema legs and had subnephrotic proteinuria on urine examination. They were classified as those with asympomatic urinary abnormalities. The most common biopsy finding in this group was mesangial proliferation followed by IgA nephropathy, focal endocapillary proliferative glomerulonephritis and minimal change disease.

Patients with focal proliferative glomerulonephritis and minimal change disease with nephrotic range proteinuria received oral prednisolone therapy. Out of 5 patients with focal proliferative glomerulonephritis, 1 had complete remission of proteinuria and recovery of renal dysfunction, 3 had partial remission while 1 patient who had sclerosing glomerulonephritis in addition to focal endocapillary proliferative glomerulonephritis progressed to chronic kidney disease and became dialysis dependent within 3 months. Out of 2 patients with minimal change disease, 1 had complete remission and the other had partial remission. Patients with amyloidosis, membranous nephropathy and mesangial proliferation received anti- proteinuric measures with angiotensin converting enzyme inhibitors and statins. Out of 9 patients with mesangial proliferative glomerulopathy, 3 patients achieved complete remission, remaining 6 continued to have proteinuria during follow up.

TABLE –12. CLINICO-PATHOLOGIC CORRELATION

Renal histology	Proteinuria (Urine PCR – 1 to 3.5)	Nephrotic syndrome	Hematuria	Hypertension	Renal failure
Mes PG (n=9)	9	-	-	1	1
Foc EPGN (n=5)	5	-	3	2	2
IgA Nephropathy (n=3)	3	-	1	1	-
MN (n=2)	-	2	-	1	-
Amyloidosis (n=2)	-	2	-	-	1
MCD (n=2)	1	1	-	-	-
FSGS (n=2)	-	2	-	-	-
Others (n=2)	1	1	-		2

TABLE–13. GLOMERULAR DISEASES – OUTCOME

Renal histology	Partial Remission	Complete remission	Persistent Proteinuria	Persistent Hematuria	Renal failure at follow up
Mes PG (n=9)	-	3	6	-	-
Foc EPGN (n=5)	3	1	1	-	1 (Dialysis dependent)
IgA Nephropathy (n=3)	1	-	2	-	-
MN (n=2)	1	1	-	-	-
Amyloidosis (n=2)	-	-	2	-	1
MCD (n=2)	1	1	-	-	-
FSGS (n=2)	1	-	1	-	-
Others (n=2)	-	-	2	-	2

RISK FACTORS FOR PERSISTENT PROTEINURIA

About 27 patients who had glomerular disease in biopsy were followed up and found that proteinuria was persistent in 14 patients. Among remaining 13 patients, 6 had complete remission and 7 had partial remission. Risk factors contributing to persistent proteinuria were analyzed and presented in table – 14. The more the duration of the disease and more the ESR at presentation and follow up were significantly associated with persistent proteinuria. While C-Reactive protein was also high in the persistent proteinuria group, it did not achieve statistical significance in the present study. Patient's age and gender did not really predict remission of proteinuria. The basic pathology also correlated well with persistent proteinuria as seen with amyloidosis and FSGS. But the number is too meager that statistics could not be considered.

TABLE – 14 :
ANALYSIS OF FACTORS PREDICTING PERSISTENT PROTEINURIA

Factors	Proteinuria remitted (n=13)	Persistent proteinuria (n=14)	p – value
Mean age (years)	41.3	39.2	0.62*
Female: Male	11/2 (5.5 : 1)	8/6 (1.3 : 1)	0.2#
Mean duration of RA (Years)	3.61	10.9	0.03*
Mean ESR (mm in 1st Hr)	33.8	73.2	0.0001*
Mean CRP (mg/L)	10.22	12.95	0.106*

*- Unpaired t test; #- Fisher's exact test

CHRONIC KIDNEY DISEASE AT PRESENTATION

About 23 patients presented with chronic kidney disease at entry into study. This cohort had about 12 males and 11 females. All of these patients had no urinary abnormalities. Their ultrasonogram of the kidneys showed grade III echoes and altered cortico-medullary junction. Hence renal biopsy was not considered in these patients. The profile of this group is shown in the following table.

TABLE – 15	
Patients with chronic kidney disease N (%)	23 (44.2%)
Age in years (mean $\pm$ SD)	50 $\pm$ 10.3
Male : Female	1 : 1
Duration of rheumatoid arthritis in years (Mean)	11.1
Mean C- Reactive Protein (mg/L)	8.9
Mean Serum creatinine at entry (mg/dl)	2.0
Mean eGFR at entry (ml/mt/1.73m^2)	36.5
Mean serum creatinine at follow up (mg/dl)	2.46
Mean eGFR at follow up (ml/mt/1.73m^2)	31.1

Most of the patients were in CKD stage III B according to the latest KDIGO - CKD classification. On follow up, only 7 out of 23 showed a significant decrease in eGFR and worsened to the next stage of CKD. Rest of the patients remained in the same stage with relatively stable GFR. None of the patient reached stage V CKD. The proportion of patients in various stages of CKD is shown in table - 16

TABLE – 16		
CKD- STAGE	Number of patients (n = 23)	
	At entry	At follow up
I	-	-
II	1	-
IIIA	2	2
IIIB	15	10
IV	5	11
V	-	-

DISCUSSION

Renal involvement in rheumatoid arthritis (RA) can remain asymptomatic as evidenced by the present study in which about 27 patients (52%) did not have renal symptoms and they have been detected to have either urinary abnormalities or raised serum creatinine or both only on screening. The mean age group of patients studied was 45.1 years, with a peak in the third and fourth decade. The female: male ratio in the present study was 1.5 : 1, which is slightly less than the usually reported ratio[1] of 2.5 : 1. The duration of illness varied from 6 months to 30 years with a mean of 8.5 years. The renal involvement in RA increases proportionally with the duration of the disease as evidenced by more occurrence of microalbuminuria in those with longer duration of disease[45]. Almost all patients had elevated ESR at entry into study with a mean of 54.8 mm in 1 hour. The mean C- reactive protein was also high at 10.6 mg/L. Raised ESR and CRP suggests increased disease activity and the more likelihood of developing renal disease.

CLINICAL PRESENTATION

About 52% of patients were asymptomatic at the entry into study. The most common symptom was edema of the legs (29%), followed by reduced urine output (13.4%). Macrohematuria was rare and occurred in only 2 out of 52 cases (3.8%). Hypertension was detected in 11 patients (21%). In the necropsy series reported by Boers et al[16], which included 132 cases, about 26 (19.7%) had urine abnormalities with normal renal function and 27 (20.5%) had normal urine with loss of renal function.

About 8 patients (13.4%) presented with nephrotic syndrome, of which 3 patients also had evidence of renal dysfunction. About 4 patients (7.6%) presented with nephritic syndrome

with evidence of microhematuria and sub-nephrotic proteinuria. Asymptomatic urinary abnormalities were seen in 12 (23%) and renal failure without urinary abnormalities occurred in 23 (44.2%). A small comparison of the clinical features of the present study with that of Yoshida et al[46] is presented in the following table.

Clinical feature	**Present study. N(%)**	**Yoshida et al[46]. N(%)**
Number of patients	52(100%)	31(100%)
Nephrotic syndrome	8 (13.4%)	17 (54.8%)
Sub-nephrotic proteinuria	15 (28.8%)	5 (16%)
Microhematuria with proteinuria	4 (7.6%)	2 (6.4%)
Renal failure	25 (48%)	7 (22.6%)

HISTOPATHOLOGY:

Renal biopsy was done in 29 patients who had normal sized kidneys and presented with urinary abnormalities or renal failure or both. The remaining 23 patients had reduced kidney size with grade III echoes or poor cortico- medullary junction. Hence biopsy was not considered in this group of patients. The following discussion pertains to the cohort of patients who underwent biopsy.

The most common pathology noted was mesangial proliferation which was observed in 9 cases. The proliferation was diffuse in 2 and focal in remaining 7 patients. Focal endocapillary proliferation occurred in 5 cases and IgA nephropathy was observed in 3. Membranous nephropathy, amyloidosis, minimal change disease and focal segmental glomerulosclerosis were

noted in 2 patients each. A comparison of histopathologic findings of the present study and other international studies is presented in the following table.

STUDY	Mes PG	Foc EPGN	IgA N	MN	Amyloid -osis	MCD	FSGS	Vascu-litis	Others
Present Study (n=29)	**9**	**5**	**3**	**2**	**2**	**2**	**2**	**-**	**4**
Boers *et al*[16] (n=132)	-	1	-	9	15	-	5	8	120*
Yoshida *et al*[46] (n=31)	2	2	-	16	6	-	-	-	5
Helin *et al*[23] (1986) (n=39)	11	-	-	9	16	-	-	-	3
Korpela *et al*[25] (n=74)	23	-	-	13	20	-	-	-	18
Nakano *et al*[26] (n=158)	54	2	31	49	30	-	-	1	22
Helin *et al*[32] (1995) (n=110)	40	4	-	19	33	3	-	-	11

Mes PG - Mesangial proliferative glomerulopathy; Foc EPGN - Focal endocapillary proliferative glomerulonephritis; IgAN - IgA nephropathy; MN - Membranous nephropathy; MCD - Minimal change disease; FSGS - Focal segmental glomerulosclerosis.
*- 119 cases were found to have arteriosclerosis and reported by author as benign nephrosclerosis.

As far as the biopsy procedure is concerned, it was done after ensuring normal bleeding and clotting parameters. The position of the kidney was marked with ultrasound and biopsy was done. There were no major complications of the procedure noted. None of the patients developed macrohematuria and neither fluid resuscitation nor blood transfusion was required.

MESANGIAL PROLIFERATIVE GLOMERULOPATHY

This category includes glomeruli with proliferation of mesangial cells which can be focal or diffuse. As evident from the table, this is the commonest pathology reported in RA. Though the exact pathophysiology behind the development of mesangial proliferation is not clearly understood, there is evidence that it could be caused by RA itself and not by drugs. In the study by Nakano *et al*[26], the author found that about two-thirds of patients who had mesangial proliferation were not on DMARDs at all throughout the course of their illness. Koseki et al[47], undertook a prospective study in 235 patients to analyze the impact of the disease and drugs on proteinuria, hematuria and renal dysfunction. The authors found that drug induced proteinuria and renal dysfunction occurred in only 1.5% and 1.7% patients respectively. All of the 9 patients in the present study presented with sub-nephrotic proteinuria, while one had renal dysfunction.

IGA NEPHROPATHY

IgA nephropathy occurred in 3 patients in the present series. In a Japanese study by Nakano *et al*[26], 31 out of 158 patients had mesangial IgA deposits. Since the prevalence of IgA nephropathy in Japan is very high, this result should be interpreted with caution, because it may be related to the population bias. Korpela et al[25] from Finland reported about 8 cases of IgA nephropathy out of 56 patients. In our study, all 3 had sub-nephrotic proteinuria and one each had hypertension and macrohematuria at presentation.

FOCAL ENDOCAPILLARY PROLIFERATIVE GLOMERULONEPHRITIS

There were about 5 cases of focal endocapillary proliferative glomerulonephritis out of 29 biopsies (17%) in the present study. Ramirez et al[15] reported 3 such cases out of 76 patients. Helin et al[32] and Yoshida et al[46] reported 4 out of 110 and 2 out of 31 cases respectively. This

condition is quite rare and some authors consider that 50% of these cases were related to vasculitis. However our patients never had features of systemic vasculitis and all the 5 patients had varying amount of immunoglobulins like IgM, IgG and complement C3 in biopsy specimen. This pattern of immunofluorescence is against the usual pauci-immune nature of vasculitis. All the patients in this group had a test done for anti-neutrophil cytoplasmic antibodies (ANCA) and were found to be negative. One patient presented with acute nephritic syndrome with low C3 and normal C4. He had very high titres of rheumatoid factor and biopsy was consistent with focal endocapillary proliferative glomerulonephritis. The remaining 4 patients had normal complements. All the patients in this group received a short course of steroids for four weeks then slowly tapered. Only one patient did not respond and developed a rapid downhill course. She had focal proliferative and sclerosing glomerulonephritis with fibro-intimal proliferation of blood vessels. Antibodies to cyclic citrullinated peptides (anti-CCP) which is highly specific for RA, was strongly positive in her. She reached end stage renal disease within one month of onset and soon became dialysis dependent. Perhaps, she is the only patient who reached CKD-5D in this study.

MEMBRANOUS NEPHROPATHY

When the causes of secondary membranous nephropathy (MN) were considered, one would not forget the drugs used in the management of RA. Most of the literature published in the eighties and nineties reported a high incidence of MN because of the higher usage of gold and penicillamine in these patients. Nakano *et al*[26] reported 49 cases of MN out of 158 (31%). Helin et al[32] had 19 out of 110 (17%) and Yoshida et al[46] had 16 out of 31(51.6%) of MN. But the incidence of MN is coming down due to the application of newer biological agents in the management of RA. However the incidence of MN could not be completely related to gold and

penicillamine alone. The two patients who had MN in the present study were not exposed to gold, penicillamine or bucillamine. Their anti-nuclear antigen (ANA) was negative and their viral and malignancy screen were also negative. There have been various evidences to support that MN can occur in the absence of the drugs known to cause them. In the report by Nakano *et al*[26], about 9 of 49 cases did not receive any DMARDs. Honkanen et al[37], reported 4 cases of MN in rheumatoid arthritis. Only one patient received gold therapy 16 years before the biopsy. Other 3 patients did not receive gold or penicillamine. The pathogenesis of MN is complex and it is worth considering that RA itself can predispose to MN and that drugs might accelerate the development of this lesion.

AMYLOIDOSIS

Rheumatoid arthritis is the most common cause of amyloidosis in western countries. In India, tuberculosis and other chronic infective diseases still contribute significantly to secondary amyloidosis. But one should not forget secondary amyloidosis when a RA patient presents with massive proteinuria. The most common risk factor for the development of secondary amyloidosis is the duration of RA. Amyloidosis is also one of the commonest causes of renal dysfunction in RA. There are only 2 cases of amyloidosis in the present study. Helin et al[32], reported the highest incidence of amyloidosis which occurred in 33 of 110 (30%). Nakano et al[26] reported 30 of 158 cases (19%). Both of the patients who had amyloidosis in the present study had more duration of the disease, more severe joint involvement with deformities and both had nephrotic range proteinuria. One patient had renal dysfunction and continued to have renal failure on follow up. Poor prognostic factors include cardiac involvement and serum creatinine level greater than 2.0 mg/dL at presentation[29]. Since there is no effective treatment for secondary amyloidosis, the mainstay of management is aggressive treatment of rheumatoid arthritis.

MINIMAL CHANGE DISEASE AND FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Helin et al[32] reported 3 cases of minimal change nephropathy. Minimal change disease (MCD) can occur as a complication of NSAID as well. There were 2 patients with MCD in the present study. Both patients were taking NSAID for more than 4 years. It is very difficult to ascertain whether the disease itself or NSAIDs played the role in the pathogenesis of MCD. There were not much of reports of focal segmental glomerulosclerosis (FSGS). The present study includes 2 patients out of 29 with FSGS. Freidman et al[48] reported a case of rheumatoid arthritis who presented with nephrotic range proteinuria and did not receive any of DMARDs. The renal biopsy in this patient showed focal segmental glomerulosclerosis. Adu et al[24] studied about glomerular lesions in 10 patients and found focal segmental glomerulosclerosis in one patient.

It is not known whether RA itself causes FSGS or it is the end result of some other glomerular disease manifesting as FSGS. The present study and the few case reports highlighted just provide an idea that MCD and FSGS can occur in rheumatoid arthritis.

OTHER MISCELLANEOUS LESIONS

Tubulo-interstitial disease occurred in two patients. One patient who had acute interstitial nephritis had history of consumption of indigenous medicines, the nature of which is not known. This patient also consumed NSAIDs before the onset of renal failure. This patient recovered with conservative management. Other patient had acute tubular injury (acute tubular necrosis) and did not have history suggestive of volume loss. He also recovered with conservative management. Nakano et al[26] reported 2 cases of tubulo-interstitial nephritis and Helin et al[32] had one case of acute interstitial nephritis in his case series.

One case of nodular glomerulosclerosis has been identified in 65 year old gentleman in the present study who is not a known diabetic. He presented with nephrotic range proteinuria and renal dysfunction. Renal biopsy revealed Periodic acid Schiff positive, weak silver positive nodular mesangial expansion that was congo red negative and appeared blue on trichrome. His glucose tolerance test and $HbA1_c$ were well within normal limits. One other patient had 30 year history of RA and presented with subnephrotic proteinuria and renal dysfunction. He was not a hypertensive. His biopsy showed moderate thickening of blood vessels suggestive of arteriosclerosis and ischemic sclerosis of the tuft. In a study by Ramirez et al[15], the authors analyzed the renal pathology in 76 RA patients against an age and sex matched controls. They found marked intimal proliferation of arterioles in RA group (30%) without hypertension. This led the authors to conclude that arteriosclerosis can complicate RA even without hypertension and it may be the cause of compromised renal function in RA.

VASCULITIS IN RHEUMATOID ARTHRITIS

Vasculitis occurring either as renal limited or with systemic involvement is not uncommon in RA. Harper et al[40] reported about 10 cases of RA with vasculitis. All of them presented with proteinuria, 9 had renal dysfunction and 8 had microscopic hematuria. Renal biopsy revealed focal segmental necrotizing glomerulonephritis with extracapillary proliferation in all 10 patients. Nine patients were rheumatoid factor positive and had severe joint erosions. Five patients had features of systemic vasculitis and 4 of 5 in this group had p- ANCA positivity. Qarni et al[66] also reported 2 cases of rheumatoid arthritis with rapidly progressive glomerulonephritis. Biopsy was consistent with necrotizing glomerulonephritis. Both of these patients had p- ANCA in their serum. However, vasculitic involvement has not been noted in the

present study. It seems prudent to consider vasculitis in a case of RA, when the patient presents with rapidly worsening renal function even in the absence of systemic features of vasculitis.

IMMUNOFLUORESCENCE PATTERN IN RENAL BIOPSY

Three patients had dominant or co-dominant IgA deposits warranting the diagnosis of IgA nephropathy. Two cases each in amyloidosis and minimal change disease and one case of nodular glomerulosclerosis did not have any immunofluorescent (IF) deposits. In the remaining cases, the most common finding was IgM with C3, followed by IgG with C3 and IgG or IgM alone. Another important feature noted was 18 of 22 cases that had IF deposits were positive for C3. Korpela et al[25] studied the immunological profile of RA patients and found that IgM, IgA and C3 were the most common IF findings.

CLINICO-PATHOLOGIC CORRELATION

This study highlights the fact that renal involvement in rheumatoid arthritis can be clinically silent, as exemplified by 27 of 52 patients (52%) included in the present study were asymptomatic. Of the 27 patients, 12 had asymptomatic urinary abnormalities and remaining 15 had raised serum creatinine without urinary abnormalities. All 12 patients who had asymptomatic urinary abnormalities underwent renal biopsy. The 15 patients who were asymptomatic and had raised serum creatinine also had reduced kidney size with increased echoes, hence biopsy was not considered in them. The renal pathology in the asymptomatic group is presented in the following table.

RENAL PATHOLOGY IN THE ASYMPTOMATIC COHORT (n=12)	
PATHOLOGY	NUMBER OF CASES
1.Mesangial proliferative glomerulopathy	8
2.IgA nephropathy	1
3.Minimal change disease	1
4.Focal endocapillary proliferative glomerulonephritis	1
5.Arteriosclerosis with ischemic glomerulosclerosis	1

In the symptomatic group, nephrotic syndrome occurred in amyloidosis, membranous nephropathy, focal segmental glomerulosclerosis and minimal change disease. Of the four cases of nephritic syndrome, 3 were due to focal endocapillary proliferative glomerulonephritis and one was due to IgA nephropathy. Hypertension occurred in 5 patients. Blood vessels were thickened in 7 patients including fibro-intimal proliferation in 2 cases. Out of this 7 patients with vascular changes, hypertension occurred in only one patient. This is another example of clinico-pathological discordance proving that rheumatoid arthritis itself can affect blood vessels.

OUTCOME AND PROGNOSIS OF GLOMERULAR DISEASES

Among the patients who had glomerular diseases, 6 had complete remission and 7 had partial remission during the follow up period. Remaining 14 patients had persistent proteinuria. Duration of the disease ($p< 0.03$) and a high erythrocyte sedimentation rate (ESR) ($p<0.0001$) were statistically significant risk factors in contributing to persistent proteinuria. Serum C-reactive protein (CRP) was also high in the persistent proteinuria group, but not statistically significant. Koseki *et al*[47] performed a prospective study to evaluate renal disease in 235 RA patients and found that serum CRP, ESR and age more than 50 years at entry correlated

significantly with persistent proteinuria. Patients with minimal change disease and focal endocapillary proliferative glomerulonephritis received oral steroids in the form of tablet prednisolone at a dose of 1mg/kg for 6 weeks then tapered over another 6 weeks. Other glomerular diseases were treated with angiotensin converting enzyme inhibitors and statins. Favourable response in the form of complete remission occurred in 3 cases of mesangial proliferative glomerulopathy and one each in focal endocapillary proliferative glomerulonephritis, minimal change disease and membranous nephropathy. Partial remission occurred in 3 cases of focal endocapillary proliferative glomerulonephritis, one case each in IgA nephropathy, membranous nephropathy and minimal change disease. Persistent proteinuria were seen in 6 cases of mesangial proliferative glomerulopathy, 2 cases of amyloidosis, 2 cases of IgA nephropathy and one case each in focal endocapillary proliferative glomerulonephritis, focal segmental glomerulosclerosis and nodular glomerulosclerosis. About 6 patients had renal failure at entry into study. On follow up, 4 had persistent renal failure with only one progressing to dialysis dependent renal failure. The four patients who had hematuria at entry ceased and none had hematuria at follow up.

CHRONIC KIDNEY DISEASE AT PRESENTATION

This discussion pertains to the cohort who presented with renal failure with reduced kidney size and increased echoes precluding renal biopsy. Total number of patients in this group was 23 (44.2%). Mean age was 50 $\pm$ 10.3 years and female : male ratio was 1 : 1. Mean duration of rheumatoid arthritis was 11.1 years. About 15 patients did not have any renal symptoms and were detected to have renal failure only on screening. About 4 patients had edema legs at presentation and 5 had hypertension. Mean serum creatinine and mean estimated Glomerular Filtration Rate(eGFR) at entry were 2 mg/dl and 36.5 ml/mt/1.73 m^2 respectively. Almost all the

patients received NSAIDs until the detection of renal failure, after which it was stopped. The dose of methotrexate was reduced according to eGFR. During follow up only 7 of 23 patients had a decline in eGFR and progressed to next stage of chronic kidney disease. Rest of the patients maintained relatively stable GFR. The mean eGFR at follow up was 31.1 ml/mt/1.73 m^2. None of the patient in this cohort progressed to end stage renal disease.

PROGNOSIS

Most of the available literature confirms a favorable outcome of renal diseases in rheumatoid patients unless complicated by amyloidosis or vasculitis related crescentic glomerulonephritis. Korpela et al[49], followed 23 RA patients with mesangial proliferative glomerulopathy and found that renal function remained stable in all patients. Kelly et al[50] recalled 21 RA patients who had hematuria at a median of 7.7 years and found normal renal function in all of them. In the prospective study of 235 patients by Koseki et al[47] with an average observation period of 42 months, found that drug induced proteinuria and renal dysfunction occurred in only 1.5% and 1.7% patients respectively. NSAIDs caused renal failure only in those who had an additional insult like dehydration or those who received diuretic therapy. Also Pederson et al[45] noted that gold and penicillamine rather than NSAIDs, contributed significantly to microalbuminuria.

CAUSE OF DEATH IN RHEUMATOID ARTHRITIS

Laakso et al[9] followed 500 males and 500 females with RA with age and sex matched controls for 10 years. During the follow up period, 31 RA patients (against one control) died from amyloidosis and 42 RA patients (against one control) died from renal diseases including chronic renal insufficiency and renal infections. These findings made the author to conclude that renal diseases significantly contribute to mortality in RA patients. This study has been published in

1986. With the invention of newer DMARDs and biological agents, renal disease as a contributor to mortality has become a rarity. The evidence comes from Institute Of Rheumatology Rheumatoid Arthritis (IORRA) cohort study, done in Japan and published by Nakajima et al[51] in 2010. The authors followed up 7926 RA patients with the observation period of 35443 person-years and reported 289 deaths in the study period. The most common causes of death were malignancies (24.2%) and respiratory involvement (24.2%) including pneumonia and interstitial lung diseases. Renal failure as a cause of death occurred only in 2 of 289 (0.6%).

NON-INVASIVE MARKERS OF RENAL INVOLVEMENT

Overt clinical presentation due to renal involvement in RA is rare and worsening renal function is also rare unless complicated by vasculitis or amyloidosis[52]. The present study and various other studies reported emphasize that majority of RA patients harbor asymptomatic renal disease. Serum creatinine[53] and creatinine clearance[54] may not be sensitive indicators of renal dysfunction in RA. Hence many researchers worked on specialized tests to identify at risk RA individuals.

1. Microalbuminuria[45] is a simple and sensitive test to detect early subclinical renal dysfunction and also drug induced renal damage in RA.
2. Salli et al[55] studied microproteinuria in RA patients using multifractional Cellogel RS electrophoresis of urinary proteins and found that 11 of 14 RA patients who tested negative for routine proteinuria showed microproteinuria.
3. Niederstadt et al[56], used a highly sensitive immunoluminometric assay to measure albumin, immunoglobulin G and α1-microglobulin in 24 hour urines of RA patients and classified into glomerular, tubular and mixed glomerular – tubular proteinuria

4. Urinary N-acetyl—glycosaminidase (NAG) is a new marker of tubular function and it is abnormally raised in renal diseases[56].
5. GFR, creatinine clearance, 24 hour urinary protein and urine sediment has been used for assessing glomerular function.
6. Tubular function was assessed by urine and serum beta-2 microglobulin, urinary NAG, urinary glucose and maximum urinary concentrating capacity.

SUMMARY

1. Total number of patients studied was 52, with a female : male ratio of 1.5 : 1.
2. About 27 (52%) were asymptomatic at entry into study.
3. About 13.4% presented with nephrotic syndrome, 7.6% with nephritic syndrome, 23% with asymptomatic urinary abnormalities, 21.2% with hypertension and 3.8% with acute kidney injury.
4. Chronic kidney disease (CKD) is also common, with 23 of 52 patients (44.2%) presented with CKD.
5. The most common renal pathology noted was mesangio-proliferative glomerulopathy followed by focal endocapillary proliferative glomerulonephritis.
6. Membranous nephropathy, IgA nephropathy, minimal change disease and amyloidosis were the other histopathologies obtained in this study.
7. IgM and C3 was the commonest immunofluorescence pattern observed.
8. Duration of rheumatoid arthritis and a high ESR correlated significantly with persistent proteinuria.
9. Only one patient in the glomerular disease group progressed to dialysis dependent renal failure.
10. Among those who presented with chronic kidney disease, majority maintained a stable GFR during the follow up period with only 7 of 23 progressed to the next CKD stage.

CONCLUSION

1. Renal involvement in rheumatoid arthritis can remain asymptomatic. Hence a well planned screening is essential to identify renal involvement early.
2. There can be a wide variety of renal diseases caused either by the disease itself or by the drugs used to treat the condition, and very often it may be difficult to differentiate between the two.
3. Renal biopsy remains the 'gold standard' procedure in diagnosing the renal pathology with certainty.
4. Mesangio-proliferative glomerulopathy followed by focal endocapillary proliferative glomerulonephritis were the commonest glomerular lesions noted in the present study.
5. Membranous nephropathy is declining, owing to the phasing out of gold and pencillamine therapy. It can still occur in the absence of exposure to these drugs.
6. Chronic kidney disease also occurs with increased frequency in rheumatoid arthritis, with majority of patients maintaining a stable GFR.

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N	AGE	SEX	WT	SYMPTOMS	DURATION OF RA	DURATION OF NSAID	PDN	METHOTREXATE	OTHER DRUGS	SHT	SKIN	JOINTS	BP	U.PRO	U.DEP	U.PCR	ESR	UREA	CREATININE	ENTRY GFR	CRP	RA FACTOR	BIOPSY IMP	FOL. U.PCR	FOL. CREAT	LAST GFR	LAST ESR
1	42	M	54.5	-	6MON	-	-	-	-	-	N	N	150/90	2+	10-15 RBC	2.5	60	48	2.4	31	13.6	>256	FOCAL PROLIFERATIVE GN, ACUTE TUBULAR INJURY	0.4	1.2	62	50
2	38	F	52	-	8Y	8	10	y	-	-	N	N	120/80	2+	-	1.8	120	32	0.8	78	8.2	72	IgA NEPHROPATHY	2.4	0.9	70	110
3	35	F	56	E,O,H	6MON	-	-	-	-	-	N	SWAN NECK DEFORMITY+	120/80	4+	20 RBC	1.8	50	40	1	69	12.8	256	FOCAL PROLIFERATIVE GN	0.9	0.9	77	40
4	36	F	49	-	5Y	5	10	-	-	-	N	N	90/60	3+	-	2.5	80	35	0.8	75	8.6	96	DIFFUSE MESANGIAL PROLIFERATION	1.8	0.7	86	80
5	50	M	50	-	30Y	30	10	Y	HCQ	-	N	BOUT. DEFORMITY+	130/80	1+	-	1.6	60	86	2.9	22	17.4	144	ISCHEMIC GLOMERULOSCLEROSIS WITH MODERATE TUBULAR ATROPHY & MODERATE ARTERIOLOSCLEROSIS	1.8	1.8	35	70
6	58	F	52	E	2Y	2	10	-	-	-	SUB NOD	ULNAR DEVIATION HANDS	160/80	4+	-	4.2	60	20	0.8	63	12	48	MEMBRANOUS NEPHROPATHY	0.19	0.7	72	50
7	21	M	55.5	E,O	3Y	1	10	-	HCQ	-	N	B/L SMALL JT ARTHRITIS	120/80	3+	8-10 epi cell	3.7	90	48	1.2	66	8.6	128	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	2.8	1.2	76	80
8	18	M	52.3	-	1.5Y	1.5	7.5	Y	SULFASAL	-	N	N	120/80	1+	2-4PC	1.3	40	26	1	88	12.5	48	FOCAL PROLIFERATIVE GN	0.8	1	89	40
9	33	F	51.8	E	3Y	3	10	Y	-	-	N	SWELLING OF PIP&MCP JOI	120/80	3+	2-4 EPI CELLS	3.9	45	30	1	65	8.5	176	MEMBRANOUS NEPHROPATHY	1.8	1.1	59	40
10	62	F	62.6	O	2Y	1	10	-	INDIGENO	-	N	N	144/96	TR	6-8 PC	0.4	50	56	1.5	38	24	72	AIN WITH ACUTE TUBULAR INJURY	0.3	0.9	64	40
11	40	F	57.2	-	6MON	-	10		-	-	SUB NOD	SWELLING OF PIP JOINTS	140/90	2+	4-6PC	2.1	50	24.4	1	68	15	>256	FOCAL PROLIFERATIVE GN	1.2	0.7	96	30
12	35	M	53.7	-	2Y	2	10	Y	-	-	N	N	140/90	2+	2-3 EPI CELL	2.3	75	76	1.1	72	8.1	248	MILD MESANGIAL PROLIFERATION	1.4	1.1	71	75
13	49	F	64	E	2Y	2	5	-	HCQ	-	N	PIP SWOLLEN & TENDER	100/70	3+	5-6 EPI CELL	3.5	40	18	0.8	86	12.5	96	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	1.2	0.9	76	20
14	38	M	67	E,O	15Y	12	10	Y	-	-	SUB NOD	ULNAR DEVIATION HANDS	100/70	3+	5-6 PC	5.9	80	48	2.1	45	24	96	AA AMYLOIDOSIS	3.4	2.4	40	80
15	49	F	68.5	-	6Y	2	7.5	-	-	-	N	B/L SMALL JT ARTHRITIS	130/76	3+	-	2.6	45	34	1.2	61	8	56	MINIMAL CHANGE DISEASE	1.2	1	74	40
16	23	F	41	E,O	2Y	-	10	-	HCQ	-	N	B/L SMALL JT ARTHRITIS	120/80	3+	8-10 RBC	3.2	100	48	2	28	16.8	>256	FOCAL PROLIFERATIVE & SCLEROSING GN WITH CHRONIC CHANGES	2.1	4.2	13	90
17	25	M	45	E,O	7Y	7	10	Y	-	-	N	SWAN NECK DEFORMITY+	120/80	4+	2-3 EPI CELL	6.8	110	24	0.8	90	13.7	240	AA AMYLOIDOSIS	3.6	0.9	80	80
18	44	F	70	H	4Y	4	10	-	-	-	N	N	120/70	2+	20-25RBC	2.4	30	28	1.2	78	7	64	IgA NEPHROPATHY	0.8	0.9	104	20
19	45	F	56.6	-	8Y	8	7.5	Y	HCQ	-	SUB NOD	PIP SWOLLEN & TENDER	130/80	1+	-	1.8	40	35	1.1	68	6	-	MILD MESANGIAL PROLIFERATION	0.23	1	75	30
20	38	F	71	-	9Y	9	10	-	-	-	N	N	140/90	2+	-	2.1	75	24	1	101	8	40	IgA NEPHROPATHY	1.4	0.9	112	60
21	56	F	59.2	-	12Y	12	5	-	HCQ	-	SUB NOD	B/L SMALL JT ARTHRITIS	130/80	2+	5-7 EPI CELL	2.2	80	30	1.1	53	8	-	MESANGIAL PROLIFERATIVE GN	1.6	0.8	73	80
22	37	F	56.8	E	7Y	7	7.5	Y	-	-	N	N	120/80	3+	2-5 EPI CELL	2.5	20	26	1	69	7	-	FOCAL MESANGIAL PROLIFERATION	0.34	1.1	63	20
23	40	F	64.7	-	6Y	6	7.5	Y	HCQ	-	N	SWELLING OF PIP JOINTS	110/70	2+	2-4 PC	1.8	28	22	1	76	6	136	MILD MESANGIAL PROLIFERATION	0.16	1.2	64	20
24	34	F	47.8	-	4Y	4	7.5	y	HCQ	-	N	PIP SWOLLEN & TENDER	120/70	1+	-	1.7	60	23	0.9	66	18	80	FOCAL MESANGIAL PROLIFERATION	1.4	0.7	85	60
25	52	F	53.9	-	9Y	9	10	-	HCQ	-	N	N	130/80	2+	10-15 EPI CELL	2.1	70	22	1.1	51	12	56	MESANGIAL PROLIFERATIVE GN	1.8	0.8	70	70
26	48	M	64.8	-	5Y	5	10	y	-	-	N	N	120/80	1+	2-7 EPI CELL	0.8	55	34	1.8	46	6	80	ACUTE TUBULAR INJURY	0.7	1	83	40
27	38	F	56.6	-	7Y	4	7.5	-	HCQ	-	SUB NOD	PIP SWOLLEN & TENDER	110/70	3+	-	2.4	40	24	1.4	49	14	-	DIFFUSE MESANGIAL PROLIFERATION	2.6	1.1	62	50
28	48	F	64.4	E	6Y	6	10	-	-	-	N	N	120/80	3+	-	3.8	60	38	1	83	12	144	MINIMAL CHANGE DISEASE	0.34	0.9	91	40
29	65	M	54	E	20Y	15	10	Y	HCQ	-	N	B/L SMALL JT ARTHRITIS	110/70	3+	-	3.5	55	45	1.6	35	16	152	NODULAR GLOMERULOSCLEROSIS, MODERATE ARTERIOSCLEROSIS	3	2.1	27	40

CKD AT PRESENTATION

N	AGE	SEX	WT	SYMPTOMS	DURATION OF RA	DURATION OF NSAID	PDN	METHOTREXATE	OTHER DRUGS	SHT	SKIN	JOINTS	BP	U.PRO	U.DEP	U.PCR	ESR	UREA	CREATININE	ENTRY GFR	CRP	RA FACTOR	BIOPSY IMP		FOL. CREAT	LAST GFR	LAST ESR
30	43	M	64.3	-	8Y	7	10	-	HCQ	-	N	N	130/80	TR	-	0.29	35	62	2.8	31	5.6	-	-		2.5	35	50
31	38	M	56.7	-	7Y	6	10	Y	HCQ	-	N	B/L SMALL JT ARTHRITIS	120/80	1+	-	0.7	25	48	2.2	37	17.2	80	-		2.4	33	30
32	56	M	63.9	E,O	16Y	14	10	-	-		N	B/L SMALL JT ARTHRITIS	130/80	-	OCC PUS CELL	0.06	40	66	3.2	23	6.9	72	-		4.2	18	60
33	56	M	67	-	13Y	9	10	Y	-	HT	N	BOUT. DEFORMITY+	140/90	TR	10-16 PC	0.7	45	54	2.2	36	22	32	-		3.5	22	70
34	48	F	56.8	-	8Y	6	10	Y	HCQ	-	N	N	110/80	NIL	-	0.8	40	56	1.9	32	11	-	-		2.1	29	85
35	55	F	54.3	-	9Y	5	10	-	-	-	N	SWELLING B/L MCP&PIP	110/80	NIL	-	0.2	65	49	2.1	26	8.4	72	-		2.4	23	45
36	50	F	59	E	14Y	14	10	Y	-	-	N	N	130/80	NIL	-	0.4	65	46	1.6	39	5.4	48	-		1.9	33	50
37	55	F	61	-	10Y	6	10	Y	HCQ	-	SUB NOD	B/L SMALL JT ARTHRITIS	130/80	NIL	-	0.08	55	74	2.6	24	16.2	88	-		2.8	22	30
38	52	F	55.2	-	10Y	7	5	-	-	-	N	N	110/80	NIL	10-15 EPI CELL	0.06	80	30	1.5	38	5.7	72	-		1.7	34	40
39	62	M	58.1	-	18Y	14	7.5	Y	-	-	N	N	120/80	NIL	1-3 PC	0.32	60	46	1.6	39	7	96	-		2.5	25	65
40	62	M	67.5	-	22Y	19	7.5	Y	HCQ	HT	N	B/L SMALL JT ARTHRITIS	140/90	NIL	-	0.13	45	48	1.8	41	4	64	-		1.9	38	70
41	25	F	53	-	2Y	1	5	-	-	-	N	B/L SMALL JT ARTHRITIS	120/80	NIL	1-2 EPI CELL	0.2	60	36	1.7	42	8	32	-		1.6	45	30
42	60	M	58.9	-	14Y	12	5	y	-	HT	N	N	140/90	NIL	-	0.2	60	34	1.6	41	6	-	-		1.9	34	40
43	27	M	64	-	4Y	2	5	-	-	-	SUB NOD	PIP SWOLLEN & TENDER	120/80	NIL	-	0.16	36	28	1.7	59	6	64	-		1.8	56	35
44	67	M	62.1	E	14Y	11	10	-	HCQ	-	N	N	120/80	1+	1-2 EPI CELL	0.43	40	86	3.7	17	6	-	-		3.5	18	55
45	45	M	66.5	-	11Y	10	10	Y	-	HT	N	B/LHALLUX VALGUS	140/90	1+	2-3 PC	0.8	80	38	1.4	63	9	96	-		2	44	40
46	54	F	62.6	-	13y	12	10	-	-	-	N	N	120/80	-	-	0.4	30	54	2.4	31	12	120	-		2.7	28	30
47	45	F	57.3	-	9Y	7	10	Y	-	-	N	N	110/70	TR	3-4PC	0.24	45	45	1.7	44	8	72	-		2	38	30
48	49	F	48.3	-	11y	9	10	-	-	-	N	N	120/80	TR	-	0.18	45	43	2.4	22	6	-	-		2.6	20	20
49	54	F	57.5	-	16Y	12	10	-	HCQ	-	SUB NOD	B/L SMALL JT ARTHRITIS	130/80	1+	1-3 PC	0.5	35	38	1.9	36	12	120	-		2.4	29	40
50	44	M	63.4	-	8Y	5	10	-	-	-	N	N	120/80	1+	-	0.7	30	29	1.6	53	8	-	-		1.9	44	65
51	58	M	58.4	E	11Y	11	10	-	-	HT	N	N	140/90	1+	-	0.32	35	43	2.1	32	8	72	-		3.8	18	45
52	47	F	60.2	-	7Y	7	7.5	-	-	-	N	B/L SMALL JT ARTHRITIS	130/80	TR	-	0.16	30	44	2.2	35	6	96	-		2.6	30	30

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3
Telephone No: 04425305301
Fax : 04425363970

CERTIFICATE OF APPROVAL

To
Dr. Muthukumar. P
PG in DM Nephrology
Madras Medical College, Chennai -3.

Dear Dr. Muthukumar. P

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Evaluation of renal lesions in rheumatoid arthritis with clinicopathologic corelation" No. 01082011.

The following members of Ethics Committee were present in the meeting held on 16.08.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai, MD Dean, Madras Medical College, Chennai-3,	-- Deputy Chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
4.	Prof R. Sathianathan , MD	-- Member
5.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
6.	Prof. C. Rajendiran, MD Director , Institute of Internal Medicine, MMC, Ch-3	-- Member
7.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
8.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
9 .	Tmt. Arnold Soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

PROFORMA

NAME: AGE: SEX:

NC NO:

Symptoms:

Edema Early morning stiffness

Oliguria Fever

Hematuria Joint pain

Duration of Rheumatoid arthritis:

Duration of NSAID use:

Methotrexate:

Prednisolone:

Other nephrotoxic drugs:

Indigenous medicines:

DM: SHT:

Other co-morbid illness:

GENERAL EXAMINATION:

Skin Pallor HT:

Joints Edema WT:

BP: PR:

CVS: RS:

P/A: CNS:

INVESTIGATIONS:

	DATE					
1	URINE					
	Pro					
	Sug					
	Dep					
2	Urine PCR					
3	Urine C/S					
4	Hb					
	TC					
	DC					
	ESR					
	PL.count					
3	UREA					
4	CREAT					
5	Na+					
6	K+					
7	CRP					
8	RA					
9	ANTI-CCP					
10	Uric acid					
11	C3					
12	C4					
13	ANA					
14	ANCA					
15	eGFR					
16	Others					

CXR PA	
ECG	

USG KUB	
RENAL BIOPSY	LM IF

FOLLOW UP:

COLOUR PLATES

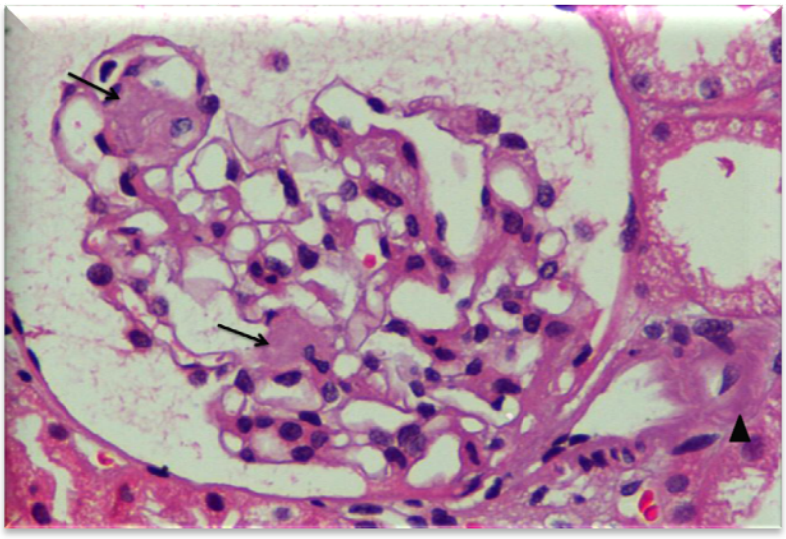

Fig-1: Renal biopsy specimen from a patient with **amyloidosis**, showing amorphous eosinophilic material in the mesangium(arrow). Similar deposit is seen over the arteriole (arrow head) [**H&E – 45X].**

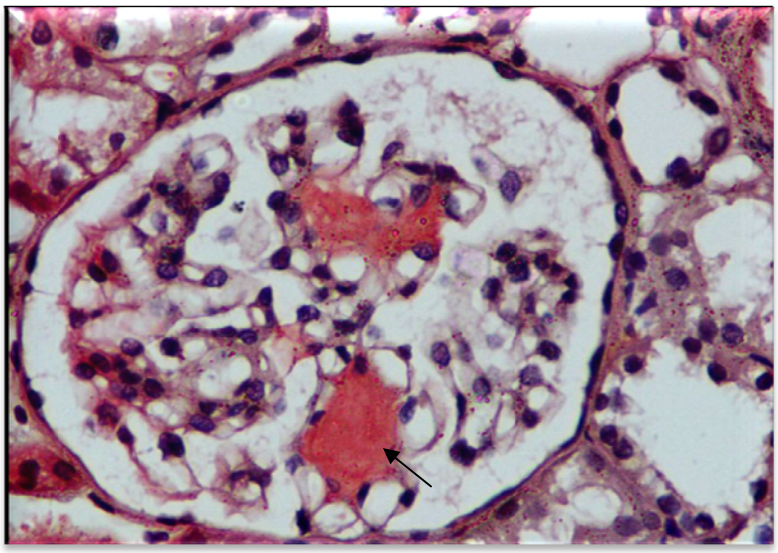

Fig-2: Strong congo red positive nodules (arrow) in the same patient with amyloidosis.**[CONGO RED 45X]**

COLOUR PLATES

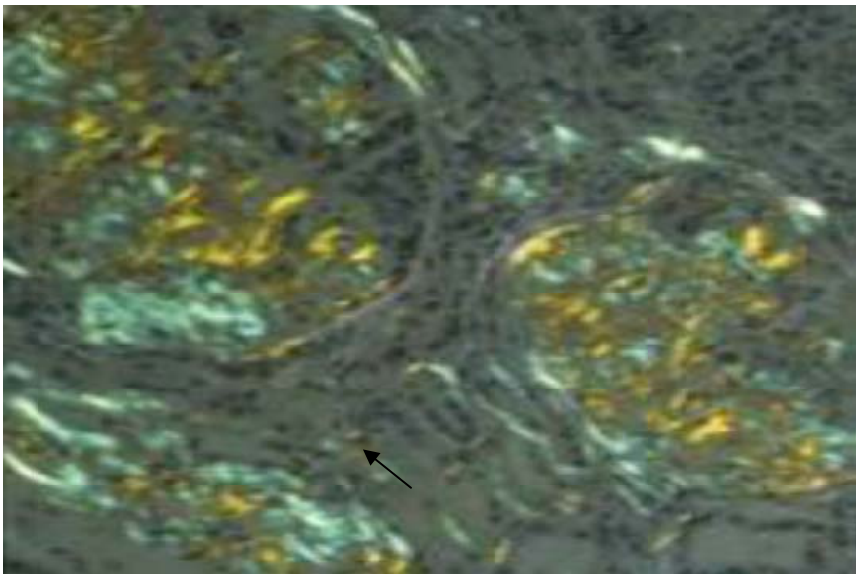

Fig-3: Congo red under polarized light showing apple green birefringence in the same patient with amyloidosis.

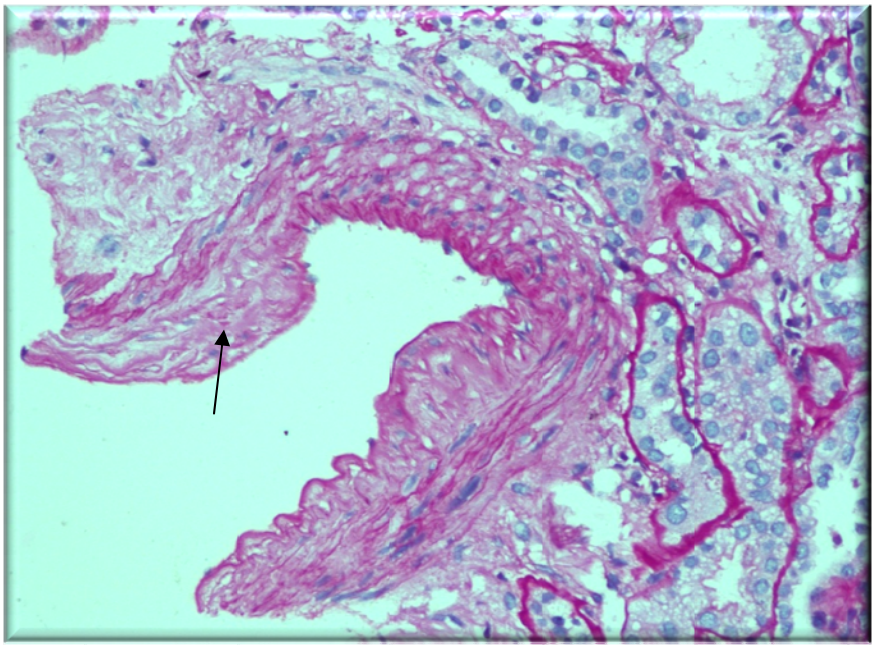

Fig-4: Fibro- intimal proliferation in a blood vessel (arrow) in a patient who had focal proliferative glomerulonephritis. **[PAS 100X]**

COLOUR PLATES

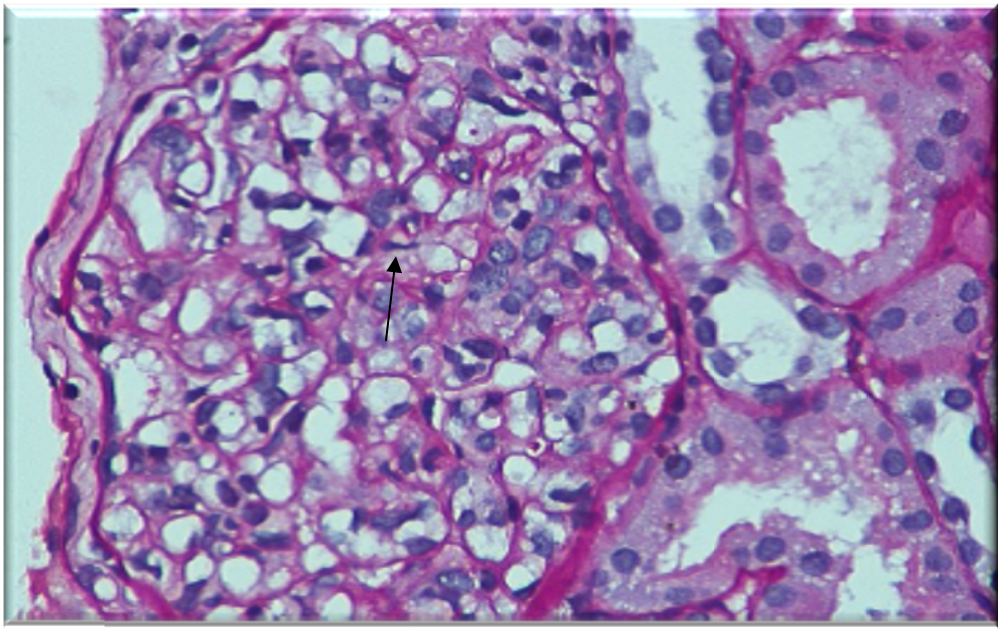

Fig-5: A glomeruli showing focal endocapillary proliferation **[PAS 45X].**

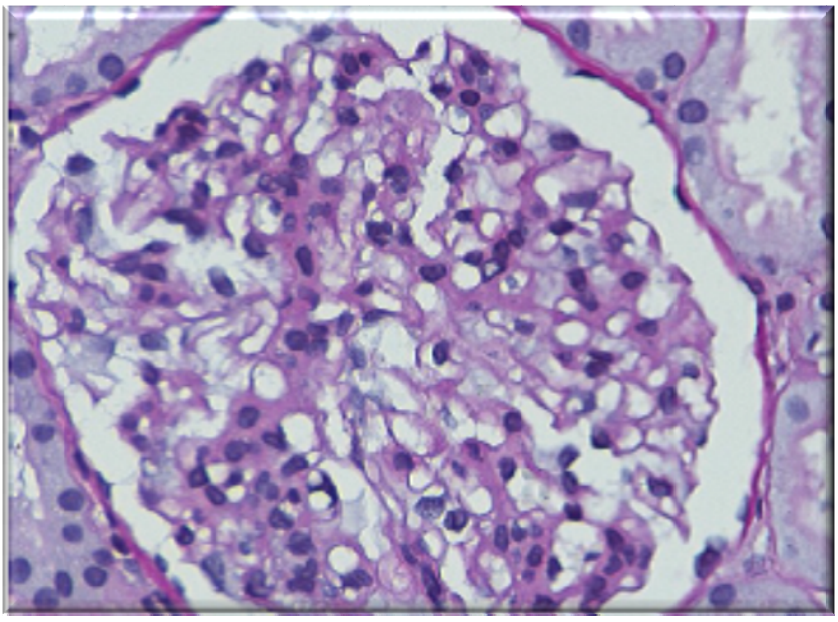

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Fig-6: A glomeruli showing diffuse mesangial proliferation.**[PAS 45X].**

COLOUR PLATES

Fig-7: Severe joint deformities of the thumb in a patient with rheumatoid arthritis who had amyloidosis in renal biopsy.

Fig-8: Swan-neck deformity in a patient with rheumatoid arthritis who had focal endocapillary proliferation in renal biopsy.

CHARTS

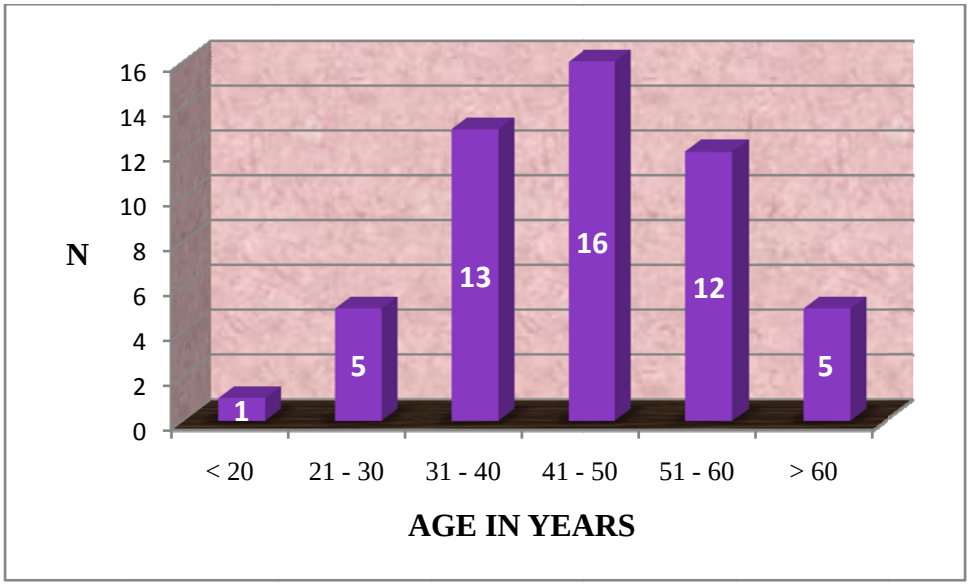

CHART NO 1: AGE DISTRIBUTION

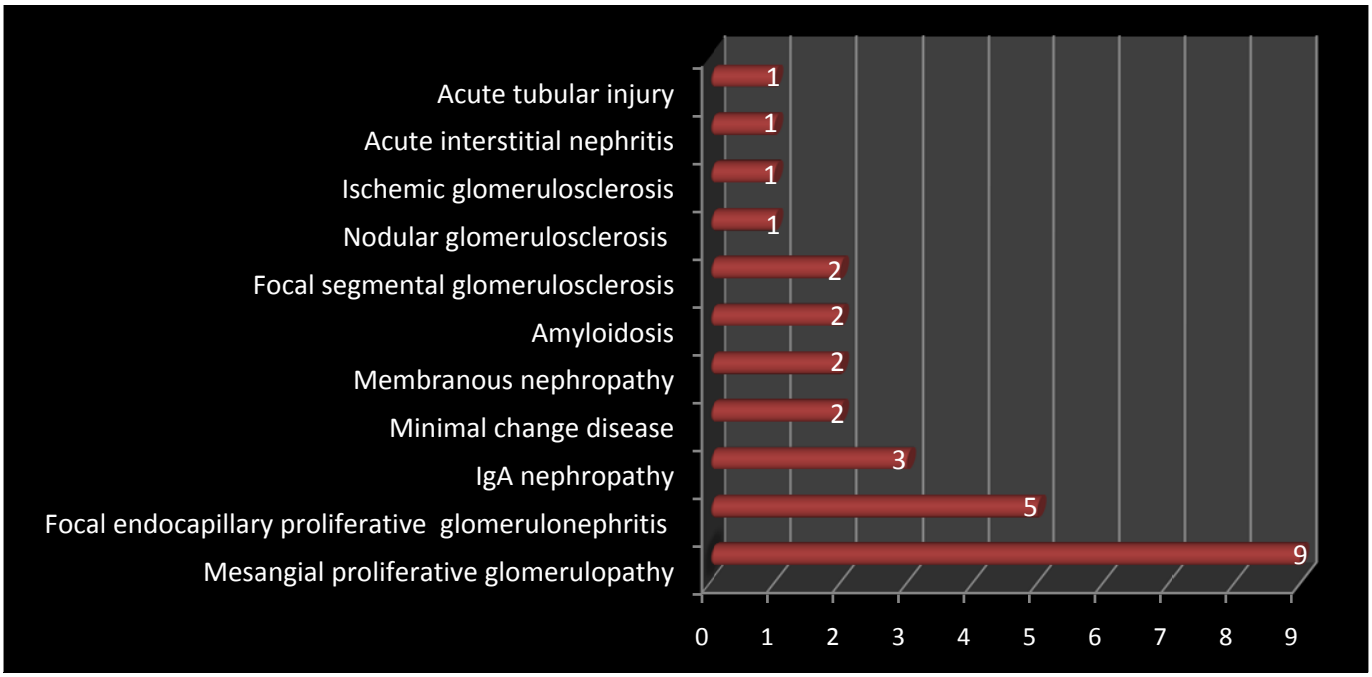

CHART NO 2 : PROFILE OF RENAL PATHOLOGIC FINDINGS